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LYMPHOSARCOMA IN BONE

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In the earlier stages extension of lymphosarcoma may take place through the lymphatics, but in advanced cases many of the organs show apparently true metastatic growths which are satisfactorily explained only on the basis of invasion of the blood vessels.[1] Reports of cases from the literature illustrate a direct extension of the disease to bones as well as hematogenous metastases.[2] Reports of larger groups of patients yield little or no information as to the incidence of involvement of the bone in lymphosarcoma.[3]

CLINICAL STUDY

The records of the Memorial Hospital for the Treatment of Cancer and Allied Diseases made available for analysis one hundred and sixty-

From the Memorial Hospital for the Treatment of Cancer and Allied Diseases. Dr. W. B. Coley, Dr. Bradley L. Coley and Dr. Douglas Quick placed their cases at our disposal in the preparation of this study.

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3. Baldridge, C. W., and Awe, C. D.: Arch. Int. Med. **45**:161 (Feb.) 1930. Goormaghtigh.[2g]

TABLE 1.—*Lymphosarcoma*

Case	Age	Sex	Duration of Disease Prior to Change in Bones	Symptoms Related to Changes in Bones (Before and After Roentgenographic Evidence)	Demonstrable Involvement of Viscera and Nodes	Involvement of Bones*	Microscopic Examination	Treatment of Bones	Laboratory Observations	Duration of Life Subsequent to Changes in Bones
1	59	F	2 years, 6 months	Tingling, numbness in fingers of right hand 1 year and 11 months before; pain in right hip 7 months before	Left femoral triangle, above left Poupart's ligament, right groin, infiltration in left cheek	Skull (C and P); right upper part of humerus (C); right scapula (C); pelvis (C); femurs (C)	Reticulum cell lymphosarcoma	High voltage roentgen therapy 12/5/30 to 6/19/31	Progressive secondary anemia; eosinophilia present	Died after 8 months, 2 weeks
2	19	F	1 year	Pain in left arm and back 6 months before; symptoms of compression of the cord 6 months before	Left cervical nodes, supraclavicular fossa, left axilla, left inguinal nodes, sternal nodes	Skull (C);left humerus (C); dorsal vertebra 12 (P); lumbar vertebrae 4, 5 (C and P); pelvis (C and P); femurs (C); bilateral pathologic fracture; tibias (C and P); left fibula (C)	Reticulum cell lymphosarcoma	Radium emanation pack, small doses 1/5/32 to 1/8/32; high voltage roentgen treatments; erysipelas and prodigiosus toxins (Coley's); transfusions	Marked secondary anemia, improved by transfusions	Died after 2 months
3	54	F	2 years	Pain in lumbar region 2 years before	Right axilla, deformity of stomach, splenic enlargement, mediastinum	Lumbar vertebra 3 (P)	Reticulum cell lymphosarcoma	Roentgen therapy	Moderate progressive secondary anemia; eosinophilia present	Died after 1 year
4	40	M	9 months	Pain in right pubic bone 9 months before; swelling of right groin 9 months before	Cervical nodes, right groin, liver enlarged, mediastinum	Right pubic bone (C)	Lymphosarcoma	High voltage roentgen therapy 8/25/31 to 9/10/31; radium emanation pack, 7/24/31 to 8/2/31	Progressive secondary anemia, slightly improved following transfusions	Died after 2 months, 2 weeks
5	62	M	4 years, 9 months	Unsatisfactory data	Left mastoid region, cervical, epitrochlear and inguinal nodes bilaterally	Right third rib (C)	Reticulum cell lymphosarcoma	High voltage roentgen therapy	Moderate secondary anemia; eosinophilia present	Living after 1 year
6	52	M	1 year	Tumor of left mandible 1 year before; deafness 3 months before	Mass extending above temporal region and downward to mandible, mediastinum	Left mandible (C)	Lymphosarcoma	High voltage roentgen therapy	Blood normal	Not followed after 6 months, 3 weeks
7	59	M	8 months	Unsatisfactory data	Right cervical nodes, right tonsil, mediastinum	Left femur (C); pathologic fracture	Lymphosarcoma	Radium emanation pack, 9/6/24 to 9/14/24	Unsatisfactory data	Died after 20 days
8	9	F	5 weeks	Mass in left cheek 5 weeks before	Mass in left cheek, nodes in left submaxillary region	Left malar bone (C)	Lymphosarcoma	High voltage roentgen therapy 8/29/27 to 5/23/28; radium emanation pack 6/14/28 to 7/2/28	Red cell count normal; moderate leukocytosis	Died after 1 year, 1 month
9	24	M	1 year, 9 months	Pain in lumbar region 9 months before; pain in interscapular region 5 months before; extensive herpes zoster on right shoulder girdle 1 week later; symptoms of compression of the cord 5 months later	Left cervical nodes, tonsils, inguinal nodes bilaterally	Thoracic vertebrae 1, 2, 3 (P)	Lymphosarcoma	Radium emanation pack 10/26/25; low voltage roentgen therapy 8/4/24 to 9/3/25	Unsatisfactory data	Died after 5 months
10	50	F	6 months	Pain in right mandible 6 months before; teeth removed at intervals before	Left cervical nodes, left axilla, left supraclavicular fossa, inguinal nodes bilaterally	Right mandible (C)	Lymphosarcoma	Radium emanation pack 2/23/24; 4/16/24 to 4/17/24	Moderate secondary anemia	Died after 2 months, 1 week
11	44	M	2 months,	Pain in lower part	Axillae, right supra-	Lumbar vertebra 4	Lympho-	High voltage roent-	Severe secondary	Died after

				before; extensive herpes zoster on right shoulder girdle 1 week later; symptoms of compression of the cord 5 months later				to 9/3/25		
10	39	F	6 months	Pain in right shoulder 6 months before; teeth removed at intervals before	Left cervical nodes, left axillia, left supraclavicular fossa, inguinal nodes bilaterally	Right mandible (C)	Lymphosarcoma	Radium emanation pack 2/23/24; 4/16/24 to 4/17/24	Moderate secondary anemia	Died after 2 months, 1 week
11	44	M	2 months, 3 weeks	Pain in lower part of back 2 months before; pain radiating down left leg 2 months before; rigidity of lower dorsal spine on admission	Axillae, right supraclavicular fossa, inguinal nodes bilaterally, mediastinum	Lumbar vertebra 4 (C)	Lymphosarcoma	High voltage roentgen therapy 4/22/30 to 10/23/30	Severe secondary anemia; moderate eosinophilia; albuminuria	Died after 7 months
12	29	M	3 months, 2 weeks	Pain in lower part of abdomen 3 months and 2 weeks before; symptoms of compression of the cord 2 weeks before	Mass in left hypochondrium, retroperitoneal nodes, mediastinal nodes, terminal ileum, diaphragmatic pericardium, parietal pleura, epidural tissues, splenic enlargement	Lumbar vertebra 2 (C); right femur (C)	Reticulum cell lymphosarcoma	High voltage roentgen therapy 6/21/29 to 6/24/29	Blood normal	Died after 3 weeks
13	24	M	6 months	Pain in left hip 3 months before	Tonsils, cervical, inguinal and axillary nodes bilaterally, submaxillary region bilaterally, swelling of left hip	Left femur (C); pathologic fracture	Reticulum cell lymphosarcoma	High voltage roentgen therapy 8/20/32 to 9/6/32; total irradiation 8/22/32 (40% S.E.D.†)	Moderate secondary anemia	Died after 6 weeks
14	11	M	6 months	Pain in left shoulder 6 months before; swelling of left scapula 6 months before	Swelling of supraspinous fossa, splenic enlargement, pelvic nodes, mesenteric nodes, jejunum, kidneys, stomach	Left scapula (P)	Lymphosarcoma	Radium emanation pack 5/1/32 to 6/10/32	Moderate secondary anemia	Died after 5 months
15	32	F	10 months	Pain in right thigh immediately before; pain about right side of head 3 months before	Generalized lymphadenopathy; spleen and liver enlarged; retroperitoneal mass felt	Femurs (C); skull (C)	Lymphosarcoma	High voltage roentgen therapy	Severe secondary anemia; differential count revealed preponderance of lymphocytes; moderate eosinophilia; moderate leukocytosis near end of disease	Died after 7 months
16	65	M	2 years, 8 months	Insufficient data	Cervical nodes bilaterally, supraclavicular fossa, axillae, spleen, liver, inguinal nodes	Pelvis (P); spine; upper end of femur (P)	Reticulum cell lymphosarcoma	High voltage and low voltage roentgen therapy	Persistent moderate leukocytosis with an increase in lymphocytes; moderate eosinophilia	Living after 1 year
17	39	M	8 months	Pain and limping 1 month before	Left supraclavicular fossa, right cervical nodes, retroperitoneal region, left inguinal and femoral area	Pelvis (C)	Reticulum cell lymphosarcoma	High voltage roentgen therapy	Blood normal	Living after 3 months

* C denotes osteoclastic; P, osteoplastic involvement.
† S.E.D. indicates skin erythema dose.

four cases in which the diagnosis of lymphosarcoma was established by biopsy or at autopsy. Seventeen patients (10.4 per cent) were found to have involvement of the bone. In every instance the changes were demonstrable prior to death.

While the duration of lymphosarcoma before and after the involvement of the bone is variable, the total duration of the disease is shorter than that usually seen in Hodgkin's granuloma. Most of the patients died before completion of the third year of the disease. In eight patients the clinical course prior to involvement of the bone gave no suggestion as to the rate of progress of the disease following osseous changes. Of eleven patients in whom change occurred in bones within one year after the onset of symptoms (table 1), eight died a few months later. Five patients had evidence of lymphosarcoma from one year and nine months to four years and nine months before involvement of bones occurred. In one patient (case 14) lesions developed in the bones before other evidences of lymphosarcoma were apparent. At autopsy the lymph nodes were found to be involved. Two patients living at the time of writing have skeletal invasion which has existed for a year. In the patients who died, demonstrable changes in bones were noted from twenty days to one year prior to death.

The age incidence does not vary from that found in the general group of patients with lymphosarcoma. Too few cases with osseous changes are available to estimate the greatest age incidence. The patients were mostly past the age of 20 years. The extremes of age were 9 and 65 years. The ratio of males to females was 1.6: 1 and was not different from that found in the general group of patients with lymphosarcoma.

Pain was an early symptom of involvement of the bone in eleven cases. The patients complained either of dull aching or of sharp lancinating pain. It could be accounted for by pressure on the nerves or by destruction of the bone. The pain was not infrequently referred down the arm or leg. Girdle pain was occasionally recorded. In one patient tingling and numbness were present in the fingers of the right hand one year and eleven months before osseous changes were demonstrated. Involvement of the mandible simulated toothache. Pain in the lower part of the abdomen was a feature in one case. This was soon followed by symptoms of compression of the cord.

Abdominal symptoms were recorded in two other cases of this series prior to death. In one patient (case 3) roentgenograms revealed a deformity about the cardiac end of the stomach. In the other patient (case 12) an abdominal exploration showed marked involvement of the terminal portion of the ileum. In a third patient (case 1) the autopsy showed infiltration of the stomach by lymphosarcoma.

The interval between the beginning of pain and the occurrence of demonstrable osseous changes varied from three months to two years.

Signs and symptoms of compression of the cord were noted in three patients. In two instances they were observed before roentgenologic evidence of invasion of the bone was obtained (cases 2 and 12). In one patient (case 9) signs of compression of the cord occurred five months after the appearance of osseous changes in the first, second and third dorsal vertebrae. In this case pain in the interscapular region preceded the changes in the bone by ten months. Extensive herpes zoster was observed about the right shoulder girdle five months previously.

Rigidity of the spine was not infrequently associated with vertebral pains.

CONSTITUTIONAL RESPONSE TO THE DISEASE

The blood picture was usually that of secondary anemia. In a few instances in which single blood counts were done the observations on the blood were normal. In the majority of patients the white cell count was normal. Transfusions temporarily improved the blood picture. The white cell count varied from that of leukopenia to that of marked leukocytosis. A detailed analysis is complicated by the repeated effects of irradiation on the hematopoietic tissues. In cases 15 and 16 leukocytosis was observed with a preponderance of cells in the lymphocytic series suggesting the development of low grade lymphatic leukemia.[4] In these two patients the white cell count showed lymphocytes ranging from 24 to 57 per cent. In fourteen cases the differential count of the white blood cells showed polymorphonuclear neutrophils ranging from 38 to 92 per cent. Ten patients were found to have from 1 to 8 per cent eosinophils. A mild leukocytosis was often reduced to a normal level by irradiation.

The urine rarely showed albumin. One patient's urine (case 16) was examined for Bence-Jones bodies and found to be negative.

In general the patients had no prolonged cachectic periods; as a rule they were in relatively good condition until near the end of the disease.

INVOLVEMENT OF THE BONE

A compilation of isolated reports of cases from the literature [2] indicates that the skull, spine and femur are most frequently involved.

In our material the bones involved were in the order of frequency: the spine, pelvis, skull, femur, humerus, tibia, scapula, mandible, fibula and ribs (table 2 and fig. 1). Pathologic fracture occurred five times. In case 2 pathologic fracture occurred in the left humerus and in both femurs.

Collapse of the diseased vertebrae was not commonly observed.

Roentgenographic Studies—Seen roentgenographically the lesions in the bones were either predominantly osteoplastic (fig. 2) or osteolytic

4. Marquio.[2e] Helly.[21]

(fig. 3). In the long bones the disease had no predilection for the part containing marrow but infiltrated the bones extensively (fig. 4). As the disease progressed, the entire bone was frequently involved. A progression of the disease was found to accentuate further the two

TABLE 2.—*Involvement of Bone in Sixteen Cases of Lymphosarcoma*

	Number of Cases	Number of Times	Right	Left
Vertebrae				
Thoracic 1	2	2	..	..
2	2	2	..	..
3	2	2	..	..
4	1	1	..	..
5	1	1	..	..
6	1	1	..	..
7	1	1	..	..
8	1	1	..	..
9	1	1	..	..
10	1	1	..	..
11	1	1	..	..
12	2	2	..	..
Lumbar 2	1	1	..	..
3	1	1	..	..
4	2	2	..	..
5	1	1	..	..
Pelvis				
Ilium	3	5	2	3
Pubis	2	3	2	1
Sacro-iliac joint	2	2	..	2
Sacrum	3	3	..	..
Ischium	..	1	1	1
Skull				
Frontal bone	2	2	..	..
Parietal bone	2	4	2	2
Malar bone	1	1	..	1
Femur				
Upper third	3	3	..	3
Lower third	1	1	1	..
Diffuse	1	1	1	..
Humerus				
Upper third	1	1	1	..
Diffuse	1	1	..	1
Tibia				
Upper third	1	1	1	..
Middle third	1	1	..	1
Scapula	2	2	1	1
Mandible	2	2	1	1
Fibula, upper third	1	1	..	1
Ribs, third	1	1	1	..

varieties of osseous change. In general, the osteolytic changes were seen more frequently.

Roentgenograms of the skull showed a predominant osteoclastic reaction (fig. 5). Small miliary or larger single punched-out areas of destruction were seen. The areas of destruction were rarely surrounded by increased bone density representing the formation of new bone.

A lesion in a rib (case 5) showed rarefaction without marked alteration in the structure of the bone.

The vertebrae showed sclerosis with some destruction of bone, occasionally with partial collapse (fig. 2). In two instances (cases 11 and 12) resorptive features predominated in the bones. A periosteal reaction about the diseased vertebrae was not seen.

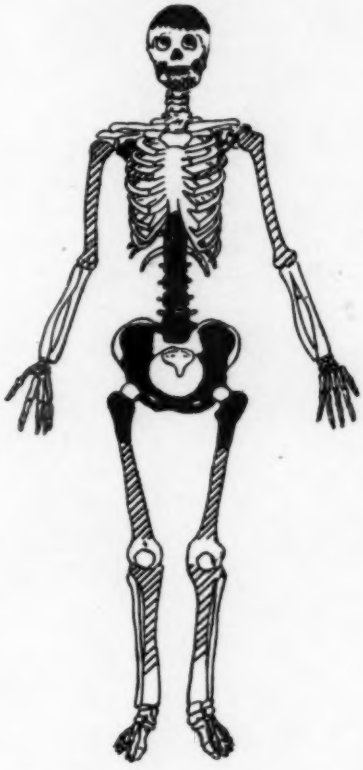

Fig. 1.—The solid black areas represent the sites most frequently involved; the checkered areas, the sites commonly involved; the diagonal lines, those invaded occasionally; the white portions, those rarely involved.

The pelvis, especially the ileum, was frequently involved. In case 2 (fig. 6) marked rarefaction with many small punched-out areas was observed in the ilium. The sacrum and fifth lumbar vertebra showed similar changes. In one instance (case 4) the pubis showed marked destruction with trabeculae not unlike a giant cell tumor (fig. 7). An osteolytic process predominated in all the pelvic lesions. The acetabula were involved less frequently than expected.

In the long bones a diffuse destructive process was common. Infiltration was the rule, often causing partial collapse of the diseased bone with fracture (fig. 4). Occasionally there was thickening of the cortex associated with a periosteal reaction (fig. 8). In some instances the destruction appeared centrally, eroding the cortex from within the

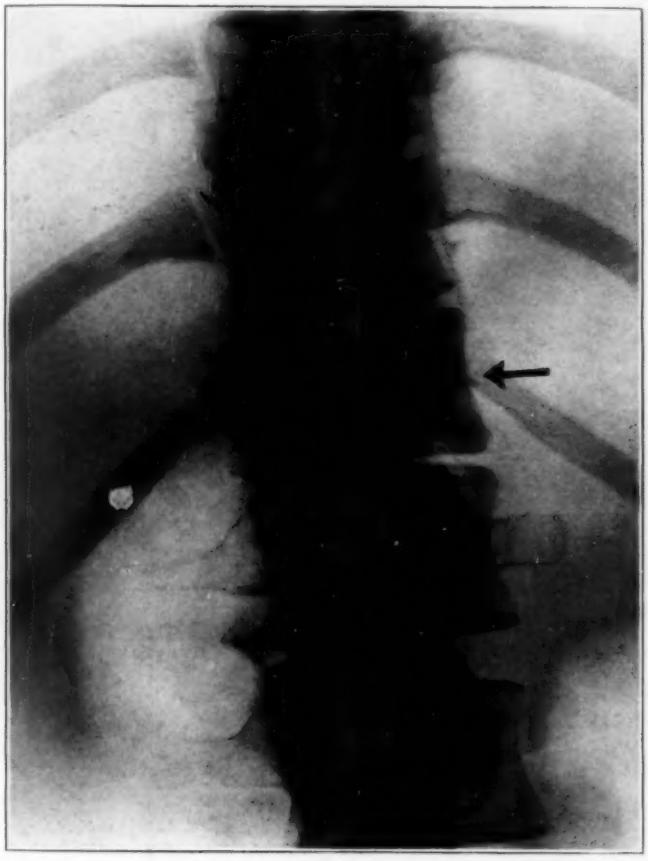

Fig. 2.—Roentgenogram depicting involvement of the twelfth thoracic vertebra. Note the predominant osteoplastic reaction. Areas of rarefaction are seen surrounded by bone of increased density.

marrow cavity. This reaction is seen in multiple myeloma and in metastatic carcinoma. The diffuse involvement of the bones with predominant osteolytic changes is characteristic of the disease. An osteoplastic reaction was noted principally in the vertebrae.

GROSS MATERIAL AND MICROSCOPIC STUDIES

A biopsy was done on every patient while under observation. A diseased gland was removed in each case. Autopsies were performed on three patients (cases 1, 12 and 14).

In case 12 the diseased femur was obtained at autopsy. The lower end of the bone was found encased in a mass of tumor which was

Fig. 3.—Roentgenogram of the scapula showing rarefaction and frank destruction along the axillary border. There is no periosteal reaction.

attached to and involved the periosteum, forming a cuff 5 cm. long and 1.5 cm. thick. The bony cortex was eroded by the tumor (fig. 9). The microscopic study (fig. 10) showed destruction of the bone by the tumor with no evidence of the formation of new bone. The tumor infiltrated through the haversian canals and extended beneath the periosteum. A mass of nodes was also found closely attached to the bone in the region of the fifth lumbar vertebra and in roentgenographic

studies this proved to be involved. This invasion of the bone was by direct extension.

In case 14 the left scapula was removed at autopsy. The supra-scapular fossa was found filled with a glistening rubbery opaque tumor

Fig. 4.—Note the diffuse involvement of the humerus. There is marked destruction with little or no formation of new bone. A pathologic fracture is seen at the upper end of the shaft. A slight periosteal reaction is seen about this area. The other humerus is normal.

mass about 4 mm. thick, extending from the acromion process across the supraclavicular fossa to the vertebral border and infiltrating the underlying bone. In both cases little or no periosteal reaction was present. Visceral lesions were found in all the cases examined at necropsy.

Fig. 5.—Roentgen ray picture of the skull showing small multiple punched-out areas of destruction. The areas of destruction were rarely surrounded by bone of increased density.

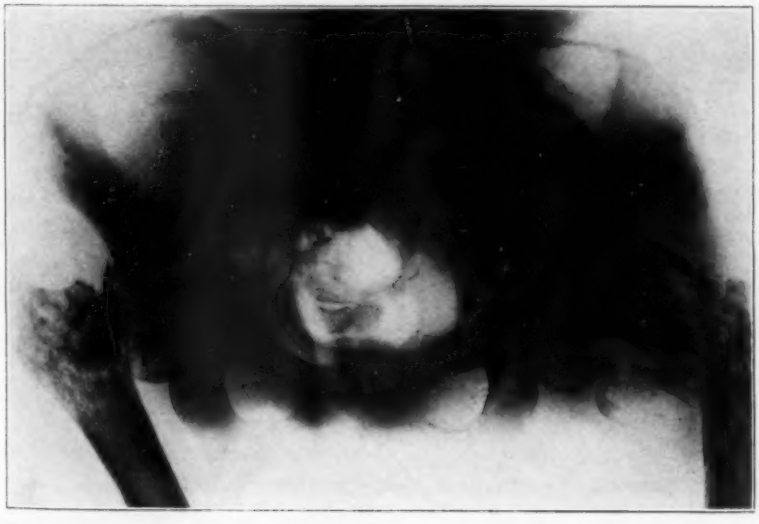

Fig. 6.—The pelvis shows marked rarefaction, especially in the left ilium, with many small punched-out areas. The sacrum and fifth lumbar vertebra show similar changes. The heads of the femurs are infiltrated and show marked destruction. Note the bilateral fracture of the femurs.

Of importance is the fact that when the tumor lies in close proximity to the bones direct extension of the disease to the bone occurs. The vertebrae are especially subject to involvement by direct extension.

Fig. 7.—Roentgenogram of the pelvis showing extensive involvement of the pubis. The trabeculations give a picture similar to that of giant cell tumor.

The microscopic appearance of the lymph nodes removed for biopsy was characteristic of reticulum cell lymphosarcoma: a diffuse growth of lymphoid cells lying in the reticular tissue. The general structure of the nodes was obliterated. The individual cells varied in size. Multinucleated cells were not observed (fig. 10).

DIFFERENTIAL DIAGNOSIS

Lymphosarcoma affecting bones may be confused with metastatic deposits in bones from carcinoma, Hodgkin's granuloma, Ewing's tumor, the leukemias and osteomyelitis.

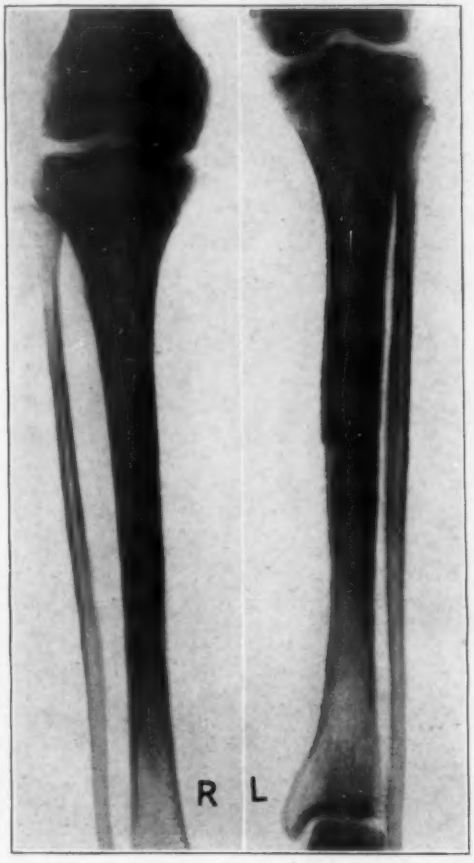

Fig. 8.—Roentgenogram of the tibias. The left tibia shows thickening of the cortex with some periosteal proliferation. Within the thickened cortex and in the upper shaft punctate areas of destruction are seen. An area of rarefaction and destruction is seen in the upper shaft of the right tibia. A periosteal reaction is visible on the lateral side of the shaft.

Varying degrees of enlargement of the lymph nodes with or without the presence of a splenic tumor are characteristic of the disease. A biopsy is of great value in establishing the diagnosis.

Metastatic carcinoma usually shows central destruction of the bone without a periosteal reaction. If seen in the earlier stages, the first

metastatic deposits are found near the point where the vessels emerge from the bone. As in Hodgkin's disease of the vertebrae and metastatic foci from carcinoma of the breast and prostate, lymphosarcoma may stimulate an osteoplastic reaction.

The leukemias may be differentiated from lymphosarcoma by studies of the blood. However, in the terminal phases of lymphosarcoma a lymphoid leukemia may develop, complicating the clinical picture, and

Fig. 9.—Photograph of bisected portion of the lower end of the femur. The lower end of the femur is encased in a mass of tumor which involves the periosteum. The cortex is infiltrated by the tumor, which also involves the marrow cavity.

there are cases of generalized lymphadenopathy in which the biopsy shows lymphosarcoma, but in which there is a low grade lymphemia and the course is similar to that of chronic lymphatic leukemia.

Hodgkin's granuloma is typified by a varying degree of involvement of the lymph node, with enlargement of the spleen, itching and secondary anemia. The changes in bones are much like those occurring in lymphosarcoma, and a biopsy of a lymph node is important for

the differential diagnosis. In osteomyelitis, especially in the early stages, destruction of the bone with a periosteal reaction may be mistaken for lymphosarcoma. The leukocyte count is of value. A sequestrum with a shaggy periosteal reaction characterizes the later stages of osteomyelitis. Atypical osteomyelitis, however, frequently requires a biopsy to establish its identity.

TREATMENT

As in Hodgkin's disease, one's main reliance in the treatment of lymphosarcoma is on irradiation. The gross lesions of the bone may

Fig. 10.—Microphotograph of reticulum cell lymphosarcoma involving the bone. The bone shows infiltration by the tumor. There is no evidence of osseous regeneration.

be treated either by single large suberythema doses or by fractional doses, with high voltage roentgen rays. Relief from pain is usually prompt. Reparative changes in the bones may be observed after treatment. In the terminal stages of the disease routine irradiation of all the bones is not attempted. This conservative attitude is taken because the severe anemia which exists in many of the late cases would only be aggravated by irradiation.

SUMMARY

1. One hundred and sixty-four patients with lymphosarcoma have been studied.

2. Seventeen patients (10.4 per cent) were found to have involvement of the bone.

3. The bones most frequently involved were those of the spine and pelvis.

4. Pathologic fracture was observed five times.

5. Collapse of the vertebrae was relatively rare. Signs of compression of the cord were noted in three patients.

6. Two types of osseous changes were noted: an osteolytic and an osteoplastic change. Osteolytic changes predominated. A combination of both was seen occasionally.

7. Two routes of involvement of the bone were observed: (1) the hematogenous route and (2) direct infiltration from contiguous diseased lymph nodes.

8. The histopathologic studies showed all the specimens to be reticulum cell lymphosarcomas.

9. The stomach was involved by lymphosarcoma in two cases; the ileum, in one case.

10. All the patients except one had evidence of involvement of the lymph nodes prior to demonstrable osseous changes.

11. In two patients a low grade lymphatic leukemia developed prior to death. Histologically the lymph nodes showed typical lymphosarcoma.

EFFECTS OF DIVERTING THE GASTRIC CONTENTS TO THE LOWER INTESTINAL LEVELS

PAUL E. McMASTER, M.D.
LOS ANGELES

As a result of much clinical and experimental work, the ulcer-producing effect of the gastric contents on the jejunal mucosa following gastrojejunostomy is well established. Few reports have been published concerning the effects of diverting the gastric contents to lower intestinal levels. This work was designed to study the results of shifting the outlet of the stomach to progressively lower levels from the duodenum to the colon, inclusive.

Rienhoff,[1] commenting on the incidence of jejunal ulcer after gastrojejunostomy, mentioned that it has occurred in as high as 25 per cent of clinical cases. He failed to find marginal ulcers following gastroduodenostomy, and having noted further that spontaneous ulceration of the third or inferior portion of the duodenum does not occur, advocated infrapapillary gastroduodenostomy in preference to gastrojejunostomy, although it is technically more difficult. After a series of experimental results in dogs, Ivy and Fauley [2] came to the conclusion that the duodenal mucosa is less sensitive to the acid gastric content than is the jejunal mucosa. They stated that if gastro-enterostomy must be done, pyloroplasty or gastroduodenostomy is preferable to gastrojejunostomy as far as postoperative ulcer is concerned. These investigators sectioned the duodenum about 1 inch (2.5 cm.) below the pyloric sphincter, then anastomosed the jejunum to the duodenum and drained the alkaline juices into the lower 15 inches (38.1 cm.) of the ileum. The acid gastric content thus came in contact with the upper duodenal and the jejunal mucosa. Of twelve dogs, eight died of perforating or bleeding jejunal ulcers. There were no duodenal ulcers.

An experimental comparison of the incidence of postoperative ulcer following gastro-enterostomy and gastro-enterostomy with duodenal drainage was made by Exalto [3] in 1911. In this study he performed gastrojejunostomy and failed to obtain jejunal ulceration in seven

From the Department of Surgery, University of Chicago.

1. Rienhoff, W. F., Jr.: Infrapapillary Gastroduodenostomy by Mobilization with Retromesenteric Displacement of the Duodenum and Jejunum, Ann. Surg. **95**:183, 1932.

2. Ivy, A. C., and Fauley, G. B.: The Chronicity of Ulcers in the Stomach and Upper Intestine, Am. J. Surg. **11**:531, 1931.

3. Exalto, J.: Ulcus jejuni nach Gastroenterostomie, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **23**:13, 1911.

dogs. In four dogs he performed a Y-anastomosis of Roux and encountered jejunal ulcers in three experiments. Following this he performed a gastrojejunostomy and then short-circuited the duodenal contents into the colon. He observed ulceration of the jejunum in each case. Leriche [4] stated that he had an occurrence of 6 per cent of jejunal ulcers after simple gastrojejunostomy, while after the Y-anastomosis of Roux the incidence was 16 per cent. Numerous investigators, such as Mann and Williamson,[5] Ivy and Fauley,[2] Matthews and Dragstedt,[6] Gallagher and Palmer [7] and Steinberg and Proffitt,[8] confirmed this high incidence of jejunal ulceration after short-circuiting the duodenal juices to the lower intestine, invaginating the upper cut end of the duodenum and performing either end-to-end or end-to-side anastomosis of the pyloric end of the stomach to the jejunum. Hence it is seen that the alkaline duodenal juices are important in the prevention of ulcer because of their neutralization of the acid gastric contents.

A marked decrease in resistance to the formation of peptic ulcer following ligation of the common bile duct was noted by Bollman and Mann.[9] In sixty-four dogs in which the common bile duct had been ligated, forty-one developed acute, subacute or chronic duodenal or gastric ulcers in from five to two hundred and ninety-five days postoperatively. Elman and Hartmann [10] drained the pancreatic juice to the outside by intubation of the pancreatic ducts in six dogs. The animals were kept in good condition by careful feeding and intraperitoneal reinjections of a "combined solution" [11] in 5 per cent dextrose. Spontaneous duodenal ulcers developed in each case. This work also illustrates the rôle of both bile and pancreatic juice in the prevention of peptic ulcer. The mechanism of this protection is probably through the neutralization of the gastric acidity by reflux into the

4. Leriche, R.: Pathogénie de l'ulcère peptique post-opératoire, J. de chir. **38**:465, 1931.

5. Mann, F. C., and Williamson, C. S.: The Experimental Production of Peptic Ulcer, Ann. Surg. **77**:409, 1923.

6. Matthews, W. B., and Dragstedt, L. R.: The Etiology of Gastric and Duodenal Ulcer: Experimental Studies, Surg., Gynec. & Obst. **55**:265, 1932.

7. Gallagher, W. J., and Palmer, W. L.: Experimental Jejunal Ulcer: Relative Importance of Mechanical and Chemical Factors, Proc. Soc. Exper. Biol. & Med. **30**:468, 1933.

8. Steinberg, M. E., and Proffitt, J. C.: The Etiology of Postoperative Peptic Ulcers, Arch. Surg. **25**:819 (Nov.) 1932.

9. Bollman, J. L., and Mann, F. C.: Peptic Ulcer in Experimental Obstructive Jaundice, Arch. Surg. **24**:126 (Jan.) 1932.

10. Elman, R., and Hartmann, A. F.: Spontaneous Peptic Ulcers of Duodenum After Continued Loss of Total Pancreatic Juice, Arch. Surg. **23**:1030 (Dec.) 1931.

11. Hartmann, A. F., and Elman, R.: The Effects of Loss of Gastric and Pancreatic Secretions and the Methods for Restoration of Normal Conditions in the Body, J. Exper. Med. **50**:387, 1929.

stomach. The neutralizing power of duodenal juices is further shown by a comparison of the work of Dragstedt and Vaughn [12] and Matthews and Dragstedt.[6] The former workers, in order to study the resistance of the intestinal mucosa to gastric digestion, made a large window in the anterior wall of the stomach. The opening was then filled with an intestinal flap taken from various levels of the bowel. The flap was prepared as follows: A segment of intestine was excised, the blood supply to it being left intact, and the continuity of the intestines was reestablished by an end-to-end anastomosis. The isolated segment was opened by an incision along its antimesenteric border and sutured into the window cut in the stomach. In this manner the mucosa of the duodenum, jejunum, ileum and colon was exposed to the gastric contents. When the segments were examined twelve months later, the mucosa of each was entirely normal macroscopically and microscopically. Matthews and Dragstedt carried out a similar procedure with a segment of colon, but in addition inserted a one-way valve in the pylorus, which, because it prevented regurgitation of the duodenal juices into the stomach, produced ulceration of the mucosa of the colon.

That the chemical action of gastric juice will produce chronic ulcer is shown by the not infrequent clinical finding of a chronic or perforated ileac ulcer at the margin of a Meckel's diverticulum containing gastric mucosa as reported by Aschner and Karelitz [13] and Lindau and Wulff.[14] With the constant finding of typical gastric glands in these diverticula it is assumed that the acid secretion from the glands is the causative factor of the ileac ulcer. By anastomosing Pavlov pouches to a spur of the ileum, Matthews and Dragstedt [6] produced experimentally in dogs ulcers similar to those found in man adjacent to Meckel's diverticulum. Chronic progressive ulcers resulted in 100 per cent of the experiments. When Pavlov pouches were anastomosed to a spur of jejunum, ulceration occurred in 85 per cent of the animals.

In 1932, Rivers and Wilbur [15] found the reports of three cases of gastro-ileostomy and added reports of seven cases from the records of the Mayo Clinic. In the three cases from the literature which they reviewed as well as in their own cases, the anastomoses had been performed by mistake, and subsequent operation was necessary for the relief of persistent or newly acquired symptoms. Of the three cases

12. Dragstedt, L. R., and Vaughn, A. M.: Gastric Ulcer Studies; The Resistance of Various Tissues to Gastric Digestion, Arch. Surg. **8**:791 (May) 1924.

13. Aschner, P. W., and Karelitz, S.: Peptic Ulcer of Meckel's Diverticulum and Ileum, Ann. Surg. **91**:573, 1930.

14. Lindau, Arvid, and Wulff, H.: The Peptic Genesis of Gastric and Duodenal Ulcer, Surg., Gynec. & Obst. **53**:621, 1931.

15. Rivers, A. B., and Wilbur, D. L.: The Syndromes of Gastro-Ileostomy and Gastro-Iliac Ulcer, Surg., Gynec. & Obst. **54**:937, 1932.

cited one showed a large, indurated gastro-ileac ulcer. Of their own seven cases gastro-ileac ulcer was found in two cases and gastro-ileitis in one. In all of the cases except one there was marked diarrhea, in some as high as from ten to twelve stools daily. Loss of weight was also a noticeable symptom.

EXPERIMENTAL WORK

The effect on intestinal mucosa, blood chlorides and body weight of dogs after the gastric content had been diverted to different levels in the intestinal tract was studied. After the stomach had been cut

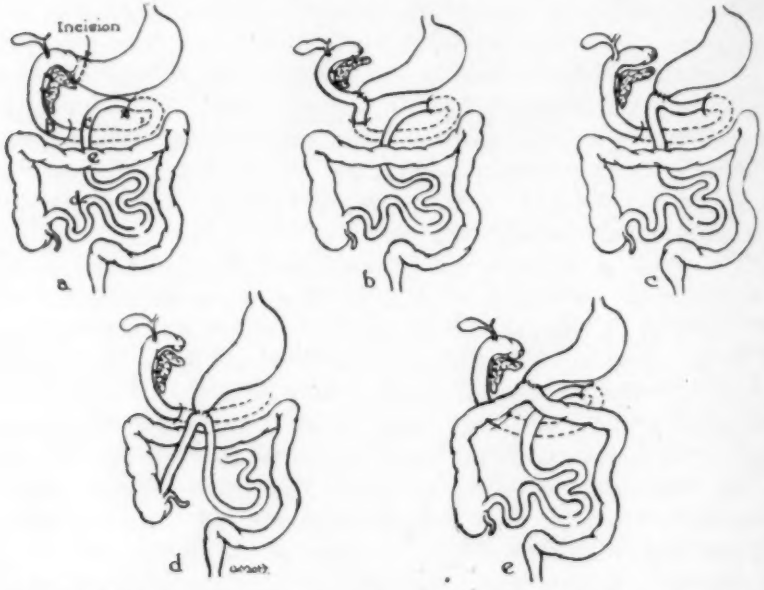

Fig. 1.—Diagrammatic illustrations showing, in *a*, the line of incision through the prepyloric portion of the stomach, and in *b*, *c*, *d* and *e*, the anastomosis of the open end of the stomach to the side of the duodenum, jejunum, ileum and colon, respectively.

through about 1 cm. proximal to the pyloric sphincter, the duodenal stump was invaginated, and the gastric end anastomosed to the side of the bowel at various levels from the duodenum to the colon, inclusive, as shown in figure 1.

Healthy adult dogs were used. Preoperative weights and estimations of the blood chlorides were recorded. Chlorides were determined as milligrams of sodium chloride per hundred cubic centimeters of blood, according to the method of Hawk and Bergeim.[16] Morphine-ether

16. Hawk, P. B., and Bergeim, Olaf: Practical Physiological Chemistry, Philadelphia, P. Blakiston's Son & Co., 1927, p. 402.

anesthesia and the usual aseptic operative technic were employed. Clamps were used only on the stomach. In approximately half of the series catgut was used, while in the other half of the experiments linen was used for suture material. In none of the cases in which linen was used was there evidence of ulceration about the material when it was examined post mortem. The ulceration which occurred was separated by a zone of mucosa from the anastomotic line; hence in this series, the material of the nonabsorbable suture had no relation to ulceration. The animals received nothing by mouth for three days postoperatively, but they were given intravenous injections of a physiologic solution of sodium chloride daily. After this, they were fed the regular stock diet of ground meat and bread, and allowed to drink fluids. Daily observations were made for vomiting or diarrhea. Weights and determinations of the blood chlorides were recorded at irregular intervals but usually once a week, unless the animal was rapidly losing weight, when more frequent observations were made.

Thirty-five experiments were performed as follows: gastroduodenostomy, four; gastrojejunostomy, eleven (the sites ranged from a few centimeters to about 60 cm. distal to the duodenojejunal junction); gastro-ileostomy, ten (including levels from high in the ileum to within 15 cm. of the ileocecal valve), and gastrocolostomy, ten (the sites included the cecum and the ascending and transverse colon).

GASTRODUODENOSTOMY

The four dogs that underwent gastroduodenostomy lost no weight; two gained weight. They all maintained the preoperative blood chloride levels, and none acquired ulceration of the duodenal mucosa when killed and examined five, seven, ten and twelve months, respectively, after the operation. Linen had been used for the suture material in three of these dogs. The anastomoses were made at levels of from 10 to 16 cm. distal to the pyloric sphincter.

GASTROJEJUNOSTOMY

Of the eleven gastrojejunostomies performed, five produced jejunal ulcers, one of which was healed and four of which were chronic or perforated (figs. 2 and 3). Most of the animals maintained their preoperative weights unless symptoms of ulcer, namely, anorexia, vomiting, listlessness and tarry stools, developed, in which event there was usually a rapid loss in weight. Blood chlorides remained essentially the same as before operation, with a few unimportant variations in some of the dogs. Table 1 gives the results for this series.

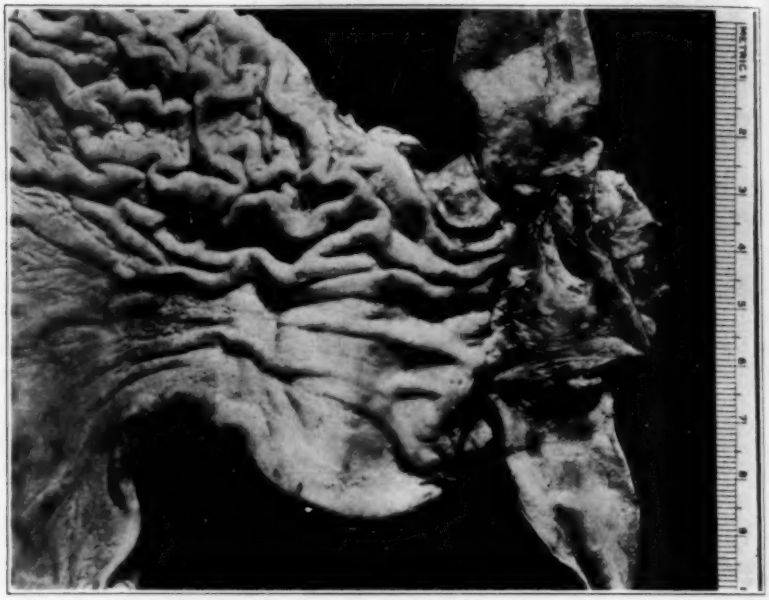

Fig. 2.—Perforated jejunal ulcer one hundred and eighty-eight days after gastrojejunostomy. The ulcer is opposite the lower part of the anastomotic stoma.

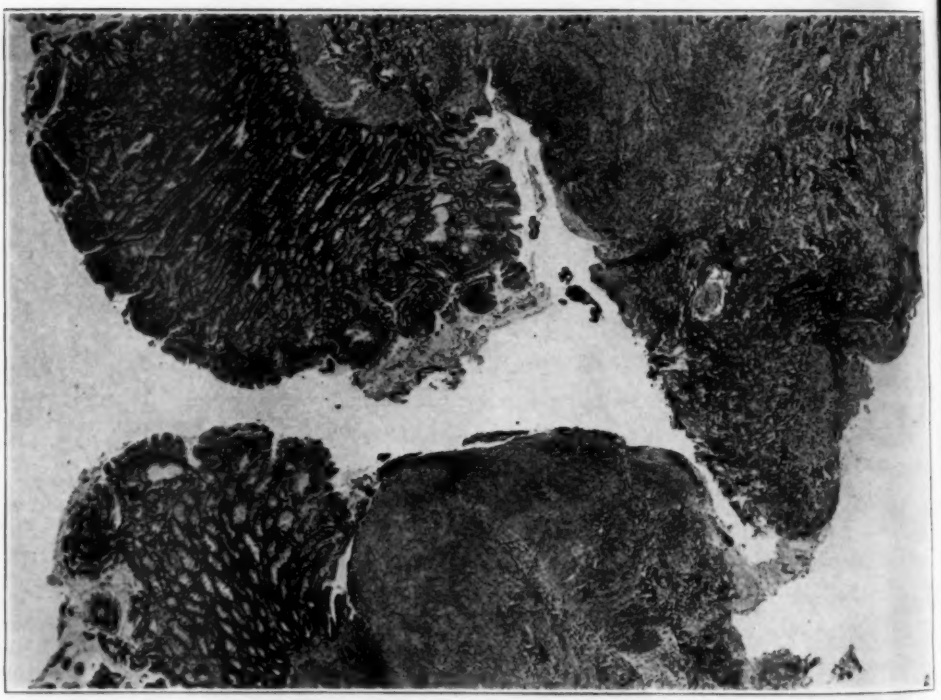

Fig. 3.—Photomicrograph of a perforated jejunal ulcer ninety-one days subsequent to gastrojejunostomy.

GASTRO-ILEOSTOMY

Seven of the ten gastro-ileostomies led to definite discrete ileac ulcers (figs. 4 and 5). One animal revealed marked, diffuse ileitis extending distally for approximately 10 cm. from the anastomosis when examined at autopsy thirty-eight days after operation. It was also noted at postmortem examination that if the anastomosis was in the lower portion of the ileum, hemorrhagic colitis was present. This was seen grossly as superficial hemorrhages and small erosions in the mucosa of the large bowel. The irritation occurred practically always in the distal half of the colon, whereas the proximal portion of the large intestine was usually free from visible signs of irritation. Microscopic

TABLE 1.—*Gastrojejunostomy*

Dog	Duration of Experiment, Days	Cause of Death	Ulcer, Jejunal	Blood Chlorides		Weight, Kg.	
				Pre-operative	Just Before Death	Pre-operative	At Death
228	307	Peritonitis; perforated jejunal ulcer	+	390	410	19.1	10.2
220	339	Killed	0	402	442	15.8	14.8
217	146	Peritonitis; 3 perforated jejunal ulcers	+	424	408	13.5	7.8
218	125	Killed	0	442	484	12.2	11.4
222	8	Distemper	0	450	436	8.4	8.0
899	54	Distemper	0	462	446	15.0	13.8
460	94	Killed	0	...	...	15.4	14.0
924	104	?; very cachetic	+ healed	442	404	11.5	5.4
493	91	Peritonitis; perforated jejunal ulcer	+	452	448	17.3	16.0
649	97	Killed	+	476	506	9.8	9.4
219	188	Peritonitis; perforated jejunal ulcer	+	450	435	12.1	6.0

sections revealed multiple hemorrhages and small erosions in the mucosa of the distal half of the colon. If the anastomosis was in the lower portion of the ileum, the animals lost considerable weight and had bloody diarrhea; the blood chloride level fell in one case to 68 per cent of the normal value. When symptoms of anorexia, vomiting, bloody diarrhea and loss of weight appeared, a diagnosis of ulcer was made and in each case verified at autopsy. Table 2 gives the results of these experiments.

GASTROCOLOSTOMY

Ten animals were used, and the anastomoses were made into the cecum or into the ascending or transverse colon. The dog in this series which survived longest lived only twenty days. The most noticeable symptom was very severe and profusely bloody diarrhea. The animals rapidly became emaciated, although a few ate well. Some refused food and water. A secondary anemia with hemoglobinometer readings of

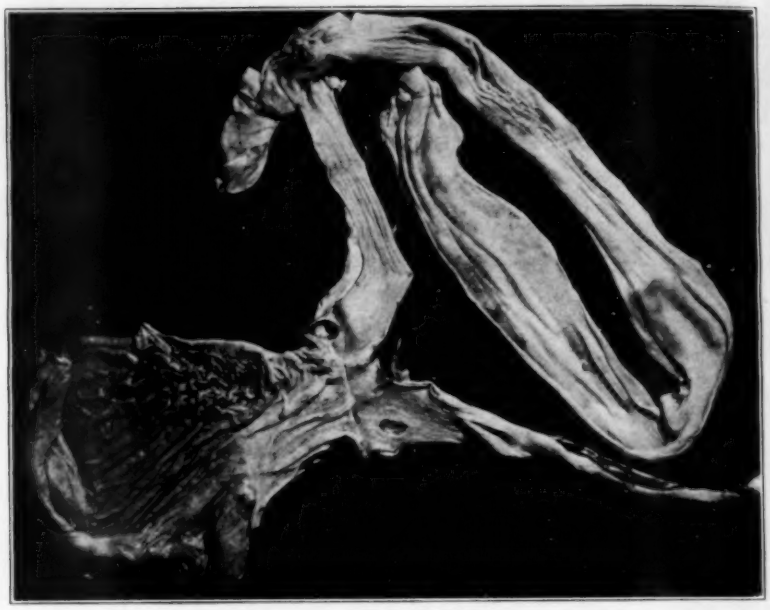

Fig. 4.—Three ileac ulcers, one walled off, one acute and one perforated, leading to peritonitis thirty-six days after gastro-ileostomy. The anastomosis is 15 cm. from the ileocecal valve.

Fig. 5.—Large chronic ileac ulcer with perforation (shown by black marker) seventy-four days after gastro-ileostomy.

TABLE 2.—*Gastro-Ileostomy*

Dog	Anastomosis from Ileocecal Valve, Cm.	Duration of Experiment, Days	Cause of Death; Autopsy Observations	Ulcer, Ileac	Blood Chlorides		Weight, Kg.	
					Preoperatively	Just Before Death	Preoperatively	At Death
285	155	69	Peritonitis; perforated ulcer	+	404	446	10.8	7.0
229	136	74	Peritonitis; perforated ulcer	+	440	480	16.4	8.9
242	105	51	Peritonitis; perforated ulcer	+	452	370	9.0	3.8
813	118	38	Distemper; diffuse ileitis	+	478	474	12.8	11.0
36	58	8	Pneumonia; acute ileal ulcers; hemorrhagic colitis	+	456	377	18.2	14.8
907	53	26	Pneumonia; slight local peritonitis from perforated ulcer	+	468	492	6.4	3.8
471	48	60	Pneumonia; hemorrhagic colitis; 1 healed ulcer in ileum	+	490	352	24.6	14.4
476	25	6	Distemper; hemorrhagic colitis	0	...	...	16.9	15.1
146	18	3	Intestinal obstruction; hemorrhagic colitis	0	424	...	26.2	24.0
45	15	6	3 ileal ulcers (1 acute, 1 walled off, 1 perforated with peritonitis); hemorrhagic colitis	+	452	310	17.8	10.1

TABLE 3.—*Gastrocolostomy*

Dog	Anastomosis, Distal to Ileocecal Valve, Cm.	Duration of Experiment, Days	Autopsy Observations	Hemorrhagic Colitis	Blood Chlorides		Weight, Kg.	
					Preoperatively	Just Before Death	Preoperatively	At Death
987	10	20	Pneumonia; hemorrhagic colitis	+	454	316	28.8	20.8
900	8	4	Perianastomotic peritonitis; hemorrhagic colitis	+	450	405	16.2	13.6
469	12	9	Hemorrhagic ulceration of colon; gastric ulcer	+	459	274	17.9	13.8
698	13	5	Pneumonia; hemorrhagic colitis	+	420	...	18.0	15.2
11	15	4	Hemorrhagic colitis; 3 acute ulcers of colon	+	456	362	29.8	26.6
46	8	3	Hemorrhagic colitis	+	448	...	18.8	16.4
49	15	9	Hemorrhagic colitis; hemoglobin just prior to death, 45 mg. per 100 cc.	+	416	332	25.4	20.4
215	10	11	Hemorrhagic colitis; hemoglobin just prior to death, 40 mg. per 100 cc.	+	483	194	11.2	6.3
986	8	2	Slight local peritonitis	+	...	...	17.5	16.2
50	12	7	Anastomotic leak; local peritonitis; hemorrhagic colitis	+	462	230	22.0	14.0

40 and 45 per cent was noted in two dogs, and another had a hemoglobin reading of 50 per cent. Determinations of the blood chloride declined rapidly and in one case dropped to 40 per cent of the initial figure shortly before death. At autopsy marked hemorrhagic colitis with numerous superficial hemorrhages and erosions, as well as free blood in the lumen of the colon, was seen grossly in each case. The proximal half of the colon was involved only once in this severe case of colitis, while in the other cases, even though the anastomoses were in the proximal portion, there was no irritation near the stoma or in the proximal half of the large bowel. The colitis extended to the anus. Microscopic examination of the hemorrhagic areas showed many mucosal hemorrhages and small erosions. In one animal a large acute ulcer of the pyloric region of the stomach was encountered. Table 3 shows the results of this series.

COMMENT

Ivy and Fauley [2] and others found that there is a higher incidence of postoperative ulcer following end-to-end anastomosis of the stomach and small intestine than following end-to-side anastomosis. In my experiments only end-to-side unions were made. Also the pyloric sphincter was not included in the end of the stomach. Thus the increased motor drive normally exerted by the sphincter was absent. This minimized the factor of mechanical trauma in the formation of the ulcers. The anastomotic stoma was made large in order to obviate gastric retention, which is thought to increase gastric acidity and predispose to the formation of ulcers.

From the results of the experiments it appears that the acid gastric content was the most important etiologic factor in the formation of ulcer. No ulceration was noted in the duodenum after four gastroduodenostomies. In these experiments the acid content of the stomach was rapidly neutralized by the duodenal juices, the formation of ulcer thus being prevented. However, as the outlet of the stomach was placed at progressively lower levels in the intestines, the incidence of ulcer increased. This may be explained by an increasing sensitivity of the intestinal mucosa at progressively lower levels, by partial absorption of the neutralizing duodenal juices in the duodenum and the upper part of the jejunum, or by changes in the duodenal juices at lower levels in the intestine by which the neutralizing properties of the juices are greatly reduced. Even though the pyloric sphincter was absent at the anastomoses, which were made large, half of the ulcers in the small intestines occurred opposite the stoma. This fact lends some support to the theory of mechanical trauma as a factor in the production of

ulcers. McCann [17] and others considered mechanical factors important in their experimental ulcers.

Support is given to the acid theory of the formation of ulcer, in preference to the mechanical theory, by the condition in the duodenum and colon after operation. In the duodenum there were no ulcers, while in the colon, although practically no irritation was seen about the anastomoses, the distal portion was the seat of severe irritation. As the food which the animals ate was well ground before administration, the irritation in the colon cannot be entirely ascribed to trauma from "roughage."

If the outlet for the contents of the stomach was placed in the lower portion of the ileum or colon, the body weight and blood chlorides fell rapidly. This did not occur if the anastomosis was in approximately the upper two thirds of the small intestine, unless symptoms of ulcer developed, when it was noted that the weight fell, but the chlorides remained essentially normal.

The use of nonabsorbable suture material (linen) in half of the operations caused no mucosal irritation or formation of ulcer.

In a few of the autopsies food was found in the intestines proximal to the anastomosis, indicating a reverse peristalsis of the small intestines. Efforts were made in four experiments to show this reverse peristalsis by the administration of barium sulphate by stomach tube and roentgenologic study, but were unsuccessful.

SUMMARY

1. End-to-side anastomoses between the open pyloric end of the stomach and the progressively lower levels of the intestine from the duodenum to the colon, inclusive, were made in thirty-five dogs.

2. The intestinal mucosa was increasingly more sensitive to gastric content from the duodenum to the colon. No duodenal ulceration followed gastroduodenostomy. Jejunal ulceration was noted in five of eleven dogs (45 per cent). Ileac ulceration developed in eight of ten animals (80 per cent) after gastro-ileostomy. Each of ten dogs had marked hemorrhagic colitis subsequent to gastrocolostomy, and usually this led to secondary anemia. The mucosa of the distal half of the colon was much more sensitive to the acid gastric content than was that of the proximal half.

3. Following anastomosis of the stomach to the lower portion of the ileum or colon, the blood chlorides and the weight fell rapidly, and there was often a marked bloody diarrhea.

17. McCann, J. C.: Experimental Peptic Ulcer, Arch. Surg. **19**:600 (Oct.) 1929.

4. The acid gastric content appeared to be the most important factor in the production of ulceration of the intestinal mucosa near the outlet of the stomach. As a number of intestinal ulcers occurred directly opposite the anastomotic stoma, the element of mechanical trauma from expulsion of the contents of the stomach cannot be entirely ruled out.

5. The loss in weight in the animals with the anastomosis in the lower portion of the ileum or colon was due largely to failure of digestion and of absorption of food. This failure of digestion and of absorption of food, with resultant loss in weight, was due (1) to reduction in the intestinal surface by exclusion of the proximal small intestine, in which digestion normally occurs, and (2) to the rapid elimination of food occasioned by the increased irritability and peristalsis in the lower portion of the ileum and colon resulting from the acid gastric content.

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SELECTION OF DRAINAGE MATERIAL

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The purpose of introducing drains into wounds is to establish an exit for existing unwanted fluid or for that which is expected to form. The problem is not one of simple hydrostatics, however. Contrary to the usual idea, almost any drainage material creates a reaction in the surrounding tissue which influences both the efficacy of the drain and the ultimate healing of the wound. This varies greatly with the character of the material used. Certain features of these reactions offer a means of dealing with the complex problems of drainage belonging to the individual case.

It is my purpose in this article to demonstrate the effect on tissue of various materials used for drains. I shall then point out how an understanding of these effects gives a rational basis for selecting the material best suited for the conditions in a given case.

Obviously not all the many and varied materials that have been used for drains can be considered. It is necessary to select representative substances. Ordinary surgical gauze and surgical rubber tubing are probably the most commonly used drainage materials. For this reason and because of their widely different effect on tissue, I have chosen them as examples.

The process must first be studied in tissue not influenced by contamination with infected or irritating material. The knowledge of fundamentals gained in this way may then be applied to the practical procedure of draining both clean wounds and those containing infected and noninfected fluids capable of irritating the tissues.

An explanation of the behavior of tissue in the presence of drainage materials involves the essentials of both primary and secondary healing of wounds. This process has been described by Hertzler in a manner readily understandable and suitable to practical application. A brief summary is inserted here. For a more detailed description the reader is referred to Hertzler's [1] two volume monograph on the peritoneum.

It was demonstrated by Hertzler that two peritoneal surfaces mildly irritated and held in apposition would be agglutinated within fifteen minutes by the formation of strands of fibrillar fibrin in the plastic lymph on the peritoneal surface (fig. 1). Mononuclear cells wander into this

1. Hertzler, A. E.: The Peritoneum, St. Louis, C. V. Mosby Company, 1919.

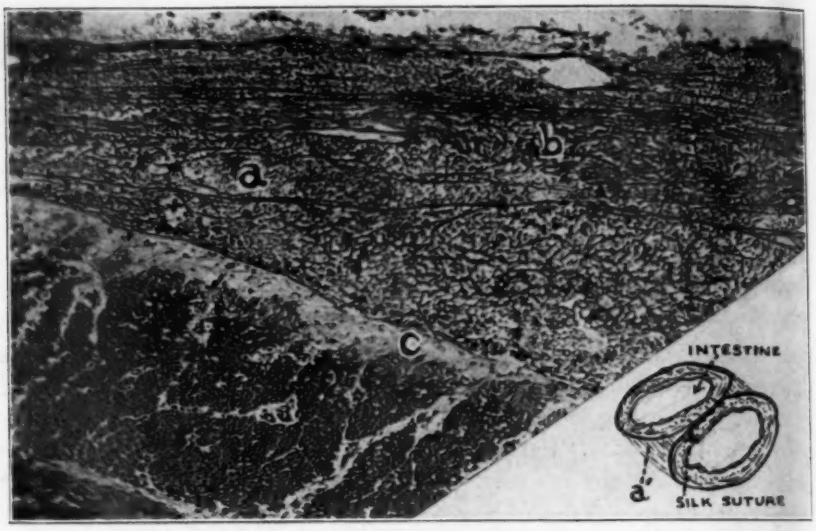

Fig. 1.—Fibrillar fibrin (*a*) found in forty-eight hours at the line of anastomosis of dog intestines. In some areas the fibrin is of only fair grade (*b*) but will organize into fibrous tissue. At *c* the edematous subserosa is seen. The insert shows how the specimen was made; *a'* represents *a* on the slide.

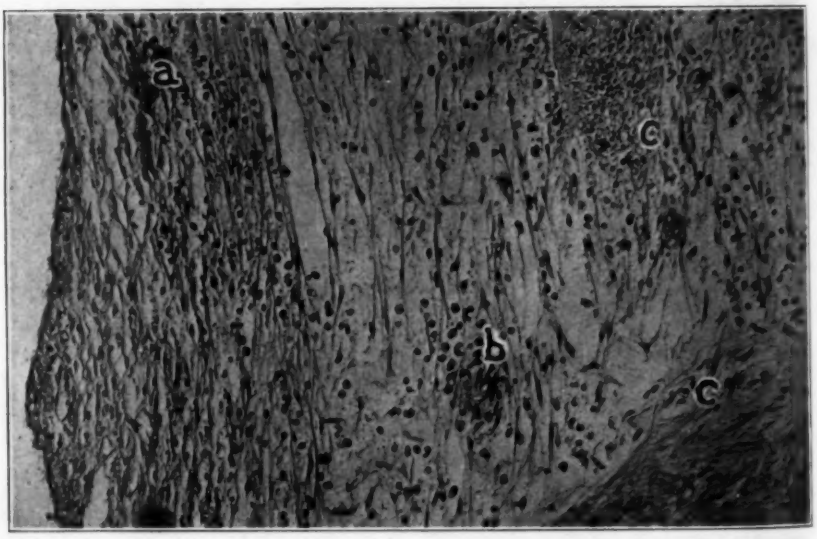

Fig. 2.—Seven day specimen of the healing line of anastomosis between two dog intestines. At *a* is a patch of poor fibrin not entirely organized. Blood vessels (*b*) are well formed in the new repair tissue; *c*, *c* is the subserosa of the intestines. Many monocytes have taken on the exact appearance of fibroblasts.

fibrillar fibrin and flatten out along the surface of the strands to become identical in appearance with the so-called fibroblast. By a chemical change the fibrillar fibrin becomes collagenous fibrin, and adult fibrous tissue thus develops (fig. 2).

Violent irritation, however, causes the formation of a granular fibrin which will not develop into fibrous tissue but must be phagocytosed before healing can be carried out. Depending on the degree of irritation, all gradations of fibrin between these extremes may be produced; a beaded type is sometimes produced which under favorable conditions will continue to develop and become reparative connective tissue (fig. 3).

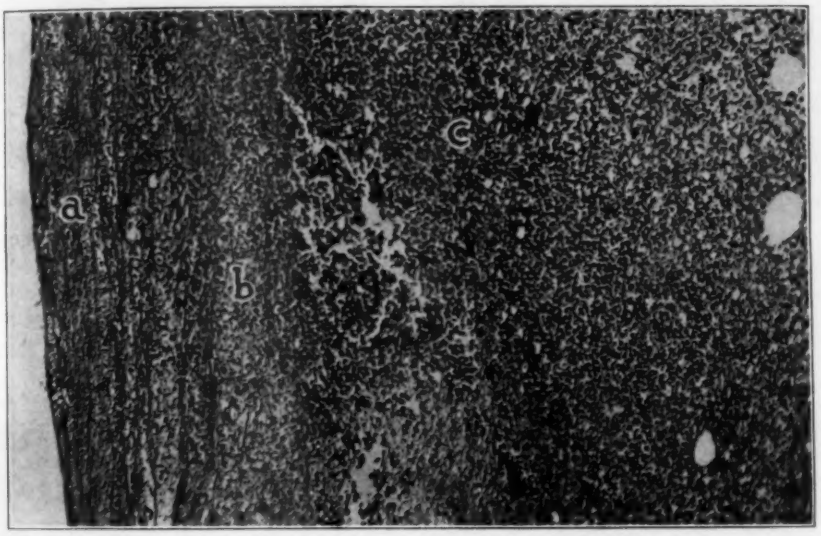

Fig. 3.—Two day specimen of the line of anastomosis between two dog intestines. Contamination with resulting violent irritation has caused granular fibrin to be formed at *c*. Near the surface, at *a*, a good grade of fibrin has developed. Between these two areas a poor grade of beaded fibrin is seen (*b*). The granular fibrin must be absorbed and replaced; *a* and *b* will develop into connective tissue.

These principles, best demonstrated in the peritoneal cavity, apply to the repair of any soft tissue.

EXPERIMENTAL PROCEDURE

In order to study the effect of rubber tubing and surgical gauze, pieces of these were tacked to the parietal peritoneum of dogs and rabbits and recovered at various intervals. This was supplemented with human material when available.

These two materials furnish two types of reactions, making it necessary to describe separately the effect of each. Neither is inert in its influence on tissue as is often supposed.

Rubber Tubing.—Specimens of rubber tubing examined grossly showed the rubber surrounded by a capsule of adjacent viscera and omentum. This capsule was lined by a pseudomembrane in contact with the rubber and having the appearance of a pyogenic membrane (fig. 4). This condition was present in twenty-four hours and did not vary even after forty days, except that the pseudomembrane became somewhat more thick and the surrounding tissues indurated.

Microscopic study showed the pseudomembrane to be formed of granulocytes and granular fibrin and identical in appearance with a pyogenic membrane (fig. 5). This was well formed within twenty-four

Fig. 4.—Rubber tubing in the abdomen of a dog after seven days. The specimen has been cut through, leaving a surface that shows a granulocytic membrane (*a*) about the rubber. The latter is easily pulled from its capsule, showing no evidence of adherence. A part of the omentum (*b*) is seen surrounding the rubber, which was sutured to the visceral peritoneum; *c* is the abdominal wall cut through in cross-section.

hours and was present even after forty days. Fibrillar fibrin was never seen in contact with the rubber but it may develop in the inner margin of the membrane in later stages.

Gauze.—Specimens of gauze examined after twenty-four hours were found surrounded with omentum and adjacent viscera. The gauze was fixed to the tissue, often rather firmly. After forty-eight hours this adherence was definitely tight (fig. 6*A*). At five days the gauze had to be torn from its bed, at times causing a slight oozing of blood. About from the sixth to the eighth day, however, a change had taken place, and the gauze could be peeled from its bed without difficulty, leaving a pale

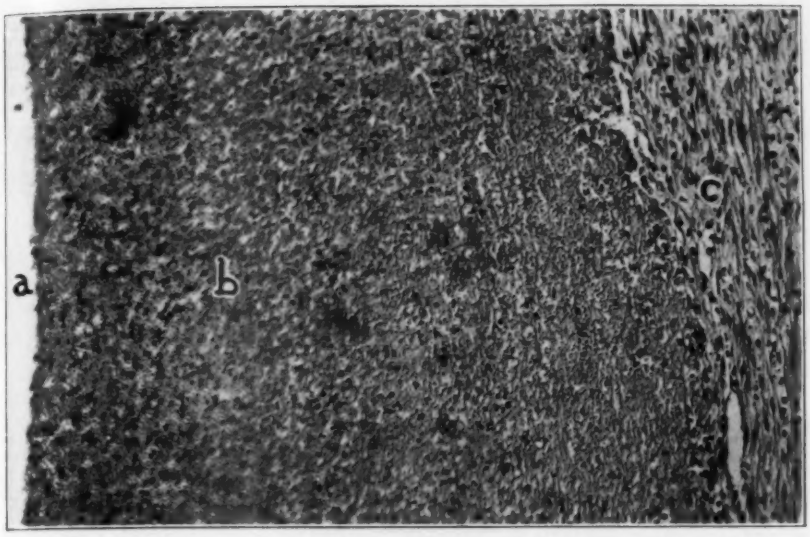

Fig. 5.—Specimen made by placing rubber tubing in contact with the parietal peritoneum of a dog (*c*) for seven days; *b*, granulocytic membrane with degenerating leukocytes near the margin in contact with the rubber tubing. The tubing was at *a* but dropped out when the section was made.

Fig. 6.—*A*, gauze pledget (*a*) in the abdomen of a dog after three days. An attempt to lift it from the tissue (*b*) showed it to be fixed; the gauze fragmented before the adhering fibrillar fibrin would release it. *B*, seven day specimen made by fixing a pledget of gauze (*a*) to the parietal peritoneum of the abdominal wall (*b*). A gentle pull on the gauze lifted it from its capsule of omentum (*c*), leaving a clean, somewhat granular, surface in the cavity (*d*). *C*, forty day specimen of gauze in the abdomen of a dog. When the gauze (*a*) was cut, it proved to be well infiltrated with tissue. When an attempt was made to draw the gauze from its capsule of omentum (*b*) it pulled apart (*a'*) before the adhering fibrous tissue would release it. The abdominal wall is at *c*.

pink, almost granular surface (fig. 6 *B*). Specimens examined at from fourteen to eighteen days showed the gauze again somewhat adherent, and at from thirty to forty days it was tightly fixed in the tissue (fig. 6 *C*).

Microscopic examination of these specimens showed that following the placing of the gauze in contact with the tissue a mild irritation resulted in permeation of the tissue with plastic lymph and the development of fibrillar fibrin. In twenty-four hours this served to fix the gauze in the tissues. After forty-eight hours monocytes had wandered along the strands of fibrin into the gauze and in four days could be seen flattening out and having the appearance of fibroblasts. Surround-

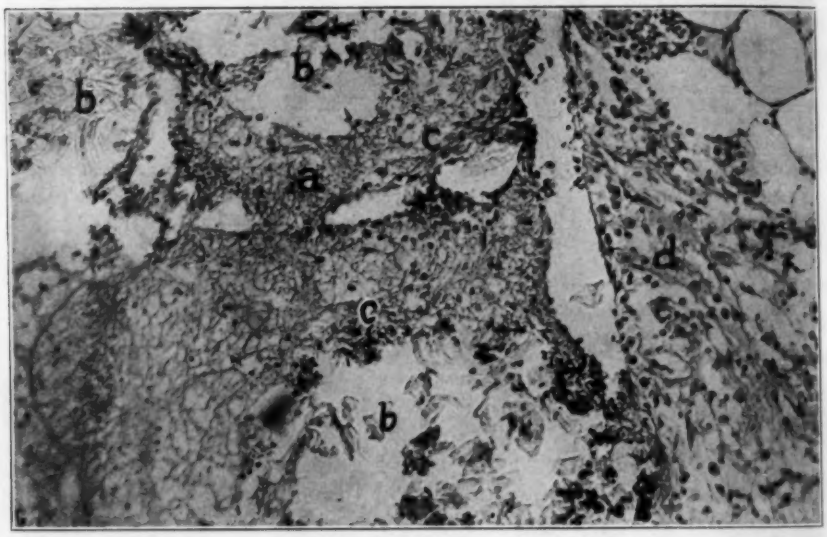

Fig. 7.—Section through a four day specimen of gauze. The fibrillar fibrin (*a*) is well formed. Many monocytes have infiltrated the surrounding omentum at *d*. Threads of the gauze are at *b*, *b*, *b*. Note the granular fibrin in direct contact with the gauze (*c*, *c*). This must be cleaned up before healing can be completed.

ing the threads of gauze was a thin area of beaded fibrin of poor grade, and in this a single layer of polymorphonuclear leukocytes was in contact with the gauze threads (fig. 7).

Six day specimens showed a disintegration of polymorphonuclear leukocytes and the beaded fibrin. Blood vessels appeared at five days, and a few foreign body giant cells were also present (fig. 8).

Between fourteen and eighteen days there was a disappearance of the débris of leukocytes and beaded fibrin, an increase in vascularity and in the number of foreign body giant cells and the formation of new fibrin between the surface of the surrounding tissue and the fibrin in the gauze. The fibrin had changed to collagenous fibrous tissue (fig. 9).

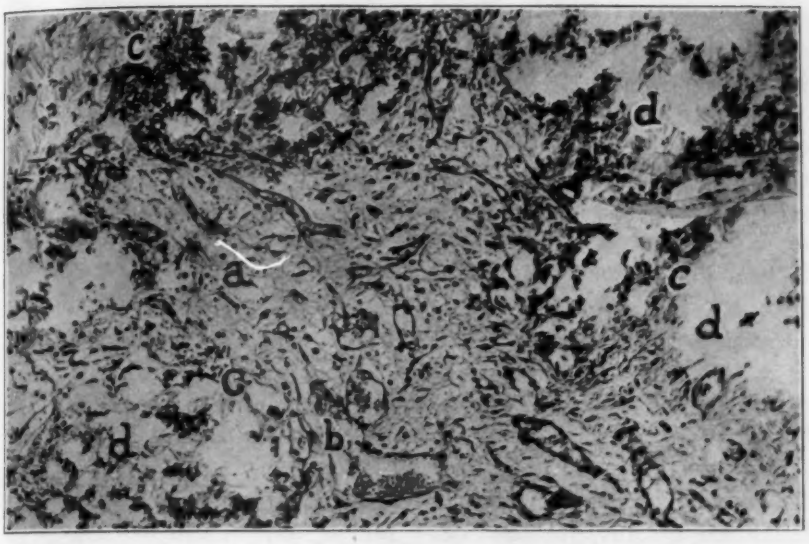

Fig. 8.—Six day specimen of gauze. The fibrillar fibrin has taken on the appearance of young connective tissue at *a*. New blood vessels have already formed at *b*. At *c, c, c* there is a débris of broken down leukocytes and granular fibrin forming a thin layer about the strands of gauze (*d, d, d*) which are loosening.

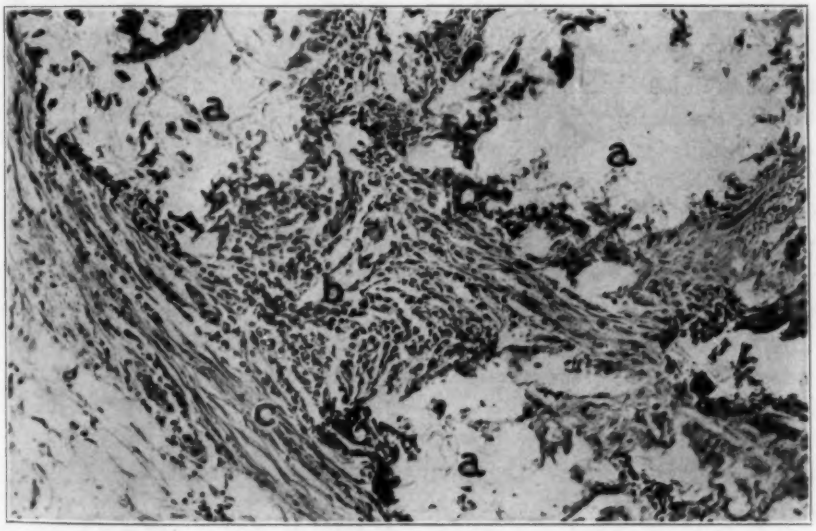

Fig. 9.—Fourteen day specimen of gauze. Well developed fibrous tissue is present in the gauze. More monocytes and fewer polymorphonuclear leukocytes are seen; *a, a, a* are threads of gauze; *b*, connective tissue; *c*, parietal peritoneum against which the gauze was fixed.

COMMENT

From the study of the rubber tubing specimens it appears that the rubber causes marked irritation of the surrounding tissue. The material used in manufacturing to give the rubber form is probably responsible for this. It serves to prevent the formation of fibrillar fibrin near it and the development of a granulocytic membrane which must be cleaned up by phagocytosis before healing can be completed. The irregular manner in which surrounding tissues stain shows that they are damaged to some extent.

If a drain of rubber tubing is placed in a clean surgical wound considerable serous drainage results. This drainage not only is incident to the surgical procedure but is in a great measure due to the failure of coagulation of plastic lymph in the wound which should seal the lymph spaces and small blood vessels. Solutions of the rubber substance prevent this, and a prolonged oozing is the result.

Moreover, when the tube is removed a pyogenic-like membrane is left lining a sinus and must delay healing until it can be cleaned up by sloughing or phagocytosis.

If rubber tubing is used to drain an infected wound this membrane may serve to retard healing after the removal of the drain until the infected débris of the deep tissues has been evacuated and the pyogenic membrane of the infected cavity cleaned up. Thus rubber tubing is a hindrance to the healing of clean wounds but an efficient drain for infected wounds.

Gauze introduced into a clean wound is likely to prove patent to the body fluids for a short time, but when removed it allows the evacuation of the clean pocketed serum and leaves behind clean surfaces covered with plastic lymph. When these fall together they quickly agglutinate, and healing progresses rapidly.

There is an added advantage in this case in that the mild irritation produced by gauze will hasten coagulation of plastic lymph in a fresh wound and promote the sealing of blood and lymph spaces. The oozing of serum into the wound is thus reduced.

Gauze used in an infected wound, on the other hand, may, when removed, result in the superficial surfaces being cleaned up quickly and in the too rapid agglutination of these surfaces with pocketing of infectious débris beneath, which has not had sufficient time to liquefy and be discharged.

A combination of drainage materials may sometimes be of advantage. Rubber placed in an infected wound in the peritoneal cavity retards the formation of protective adhesions because of its irritating properties. Gauze placed in the wound is just sufficiently irritating to encourage this process. It can be placed in the deeper part of the wound

and its end brought out to the surface. A rubber tube, the end of which rests on the gauze and is thus kept from coming in contact with the viscera, then serves to establish a tract to the surface that will remain patent until drainage is completed.

The draining of any clean wound has been repeatedly demonstrated to allow the entrance of organisms from the surface into the deep tissue within a short time. These are generally of such low pathogenicity that they have but little effect on the tissue or on the healing process. More virulent organisms convert the situation into that of an infected wound.

Pockets of blood and serum may form along the drain in a clean wound. Adherence of these surfaces to the gauze is never firm because of the failure of such large areas to coagulate thoroughly. As a result there may be areas along the gauze drain which do not become fixed at any stage.

EFFECT OF RUBBER TUBING AND GAUZE ON THE BLOOD IN THE VESSELS

As a corollary to the effect of rubber tubing and gauze on tissue a study was made of the effect of these materials on blood in uninjured vessels. Rabbits were anesthetized with sodium amytal; the internal jugular vein was isolated without traumatizing its wall, ligated and cut. Distal to, and 1 cm. from, the ligation, rubber tubing was placed in contact with the vessel in one series of animals, and gauze was used in another group. At various postoperative dates the animals were killed, the operative areas exposed, and the vessels ligated proximal to the specimens. The drainage material and surrounding tissue were then removed *en bloc* and hardened. Sections were cut through the drainage material and the vessels.

Rubber.—It was found on examination of the gross specimens that the blood in vessels in contact with rubber tubing was still uncoagulated and flowed freely from the veins if they were not ligated before the specimen was removed.

Microscopic study of forty-eight hour specimens, in which rubber had been directly in contact with vessels, showed a marked infiltration of polymorphonuclear leukocytes about the blood vessel and extending into the wall of the vessel (fig. 10). Within six or seven days the staining reaction of the vessel wall and the leukocytes showed early necrosis (fig. 11). Blood within the vessel was degenerated and showed no clotting or organization. This condition was present even after twenty days.

Gauze.—Blood in the vessels in contact with gauze was coagulated within from twenty-four to forty-eight hours. The gauze was fixed in the tissue and to the vessel wall by fibrin.

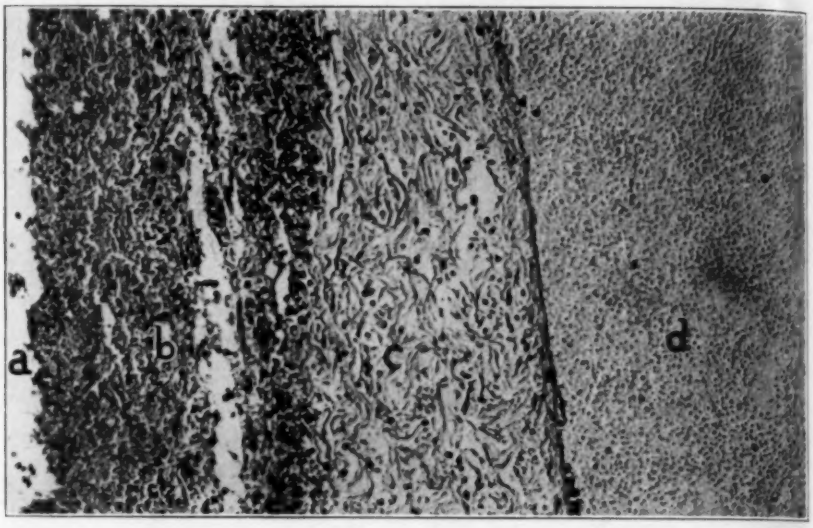

Fig. 10.—Rubber tubing was present at *a* but fell out in sectioning. It had been in contact with the blood vessel (*c*) of a rabbit for two days. At *b* is the granulocytic membrane. A few polymorphonuclear leukocytes are infiltrating the vessel wall; *d* is uncoagulated blood in the vessel.

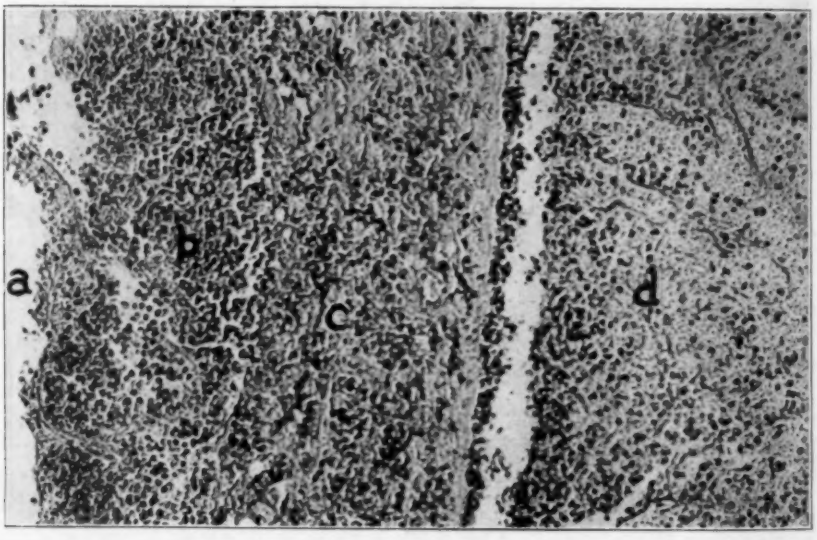

Fig. 11.—Rubber tubing was present at *a* for eight days; *b* is the granulocytic membrane; *c*, the vessel wall with early necrosis and marked infiltration of leukocytes; *d*, uncoagulated and degenerating blood. The specimen is from the neck of a rabbit.

Microscopic study of forty-eight hour specimens showed slight edema of the vessel walls. The blood within the vessel was beginning to organize as a healthy appearing thrombus. The organization extended from the wall where the gauze was in direct contact.

Nine day specimens showed the vessel filled with a rapidly organizing thrombus (fig. 12). Later stages showed a continuation of a healthy organizing process.

Ligation of a vessel may result in the rapid development of a thrombus near the point of ligation when the intima is injured, but uncoagulated blood may remain in the vessel for weeks if the intima is not traumatized in ligation.

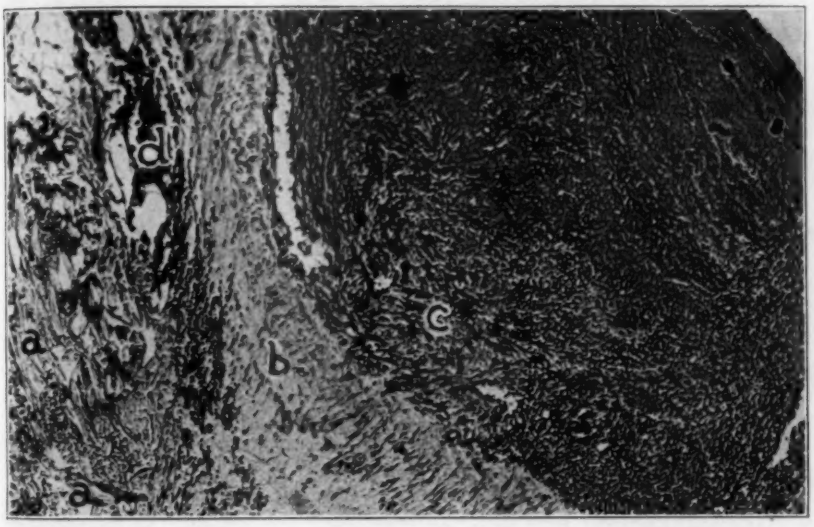

Fig. 12.—Specimen made by placing gauze in contact with a vessel in the neck of a rabbit for eight days. The gauze threads are at *a*, *a*; *b* shows a vessel wall; *c*, organizing blood clot firmly fixed to the intima of the vessel. The small lymph node at *d* is compressed by gauze against the vessel.

Hertzler demonstrated that if a mild chemical irritation was applied to the vessel wall, organization of the blood was stimulated. He also showed that application of violent irritation caused marked delay in organization, even though a clot was formed in the vessel.

Our experiments show the application of these principles in the relation of blood vessels to drainage material placed in a wound. The effect of failure of lymph spaces and small blood vessels to be sealed by coagulation in a fresh wound owing to the irritating effect of the rubber solution is readily understood. This causes an excess of serous and bloody discharge in clean wounds in which rubber tubing has been

used for drainage. Thus one may also explain the absence of this factor when gauze is used. The irritating effect of gauze is just sufficient to stimulate the development of fibrillar fibrin, with the result that blood and lymph vessels are effectively sealed.

There was a certain degree of damage to the vessel walls in contact with the rubber, in some cases amounting to actual necrosis. This required a number of days to become marked. The observation is of practical importance as it shows the easy possibility of secondary hemorrhage resulting from rupture of damaged vessels when rubber tubing has been allowed to come in contact with them over too long a period.

Space does not permit me to describe details of the behavior of tissue in the presence of some of the other more commonly used drainage materials. Scarcely any of them fail to produce a reaction. Even rubber dam is surrounded with a thin granulocytic membrane within two days after it is placed in a wound. Cellophane also produces a reaction, but one of almost negligible degree.

The discussion presented is not expected to serve as adequate direction for the handling of individual cases. It is only by study of the fundamental principles and their application to the task to be accomplished that one can expect to produce the most favorable results.

SUMMARY

1. Rubber tubing used for drains in wounds creates a granulocytic membrane on the wall of the wound where the rubber touches it, delaying healing.

2. The rubber tubing creates, by overstimulation of the tissue and by preventing coagulation, an excess amount of drainage not incident to the surgical procedure.

3. It should not be used as drainage material in clean wounds.

4. The manner of response of the tissue to rubber tubing may be an advantage in draining infected wounds.

5. In clean wounds gauze becomes fixed to the tissue after a few hours, but it is loose again in from six to eight days, and its removal is easy.

6. If the gauze is allowed to remain long past this time, it becomes firmly and permanently fixed in the tissue.

7. In clean wounds an ideal surface for rapid healing is left when the gauze is removed.

8. Rubber tubing delays formation of a thrombus in vessels, while gauze may promote it.

9. Rubber tubing may cause rupture of blood vessels if it is allowed to come in contact with them over too long a period.

OSTEODYSTROPHIA FIBROSA UNILATERALIS

REPORT OF A CASE

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The case to be reported presents an unusual unilateral skeletal lesion which shows intimate relationship to Ollier's achondroplasia, from which it can, however, be differentiated roentgenologically, histologically and even clinically.

REPORT OF CASE

History.—The patient was a girl who came under clinical observation in 1926, at the age of 7 years. She began to limp on the left side in the spring of 1924. March, 1925, she fell to the floor and sustained a fracture of the left femur. She was taken to a hospital, where a diagnosis of bone tumor or cyst was made, based on roentgenograms. Solid bony union did not occur until March, 1926, following a period of traction and fixation in a plaster cast. The patient was symptomless except for an occasional dull pain in the region of the left hip, especially when the weather changed. When she was first seen in the clinic a diagnosis of osteitis fibrosa cystica of the upper end of the femur, with a healed pathologic fracture, was made. She did not report again until October, 1932, at which time her mother stated that the left leg had been bowing progressively. In the latter part of July, 1932, she fell hard on the left arm and had a dull pain at the junction of the upper and middle thirds of the humerus. The arm swelled one-third larger than its normal size. The swelling disappeared within one week, and the pain within two weeks. No physician was consulted.

The patient was a well developed and well nourished white girl (fig. 1), who walked on crutches because of a marked deformity of the left lower extremity. The most striking objective finding was the asymmetry of the face and extremities.

Head.—There was a slight but distinct asymmetry of the face, the left side being somewhat underdeveloped. The muscular action on the left side was slightly decreased, and the patient said that she "smiled higher" on the right side than on the left. The pupils were round, regular and equal and reacted to light and in accommodation. There was no difference in the vascularity of the two halves of the face, and blushing occurred in equal degree on both ears and both cheeks. The mouth, neck, chest and abdomen were not remarkable.

Left Upper Extremity.—The left arm was thicker than the right, and there was some anterior bowing at the middle of the humerus. Palpation revealed a more diffuse enlargement of the bone; there was no tenderness. The left forearm showed a similar swelling in its upper two-thirds. The left thumb was slightly larger in circumference than the right. There was free motion in all the joints. The skin was normal, and there was no difference between the skin temperature of the right and left sides. (The upper part of the left arm was ½ inch [1.3 cm.] longer than the right and almost 1 inch [2.5 cm.] thicker.)

From the Orthopedic Department, State University of Iowa.

Left Lower Extremity.—This was atrophic in toto and, owing to the marked deformity of the thigh, was shorter than the right lower extremity. At the junction of the upper and middle thirds a marked lateral and anterior bowing of the femur was present. The bone was palpable at this level as a hard, slightly irregular tumor mass without tenderness on pressure. There was valgus deformity in the region of the knee joint. The left tibia was increased in size in the upper half and showed anterior bowing in the middle. Active and passive motions in the knee and ankle joints were normal. In the hip joint adduction and abduction

Fig. 1.—Photograph of the patient, showing the marked deformity of the left lower extremity and the slight asymmetry of the face.

and external rotation were zero; flexion was normal, and there was internal rotation of 15 degrees. (The spinomalleolar distance was 31⅝ inches [80.3 cm.] on the right, and 30¼ inches [76.8 cm.] on the left. The left leg was ¾ inch [1.9 cm.] longer than the right leg.) All the other results of physical examination were negative.

Laboratory Findings.—The Wassermann and Kahn reactions were negative. The red blood corpuscles numbered 4,740,000, the white blood corpuscles 8,400. The chemical findings were as follows: serum calcium 11.1 mg.; serum phosphorus, 3.9 mg., and phosphatase, 32.5 mg. The urinary calcium on three successive days averaged 0.94 Gm. for twenty-four hours, and the urinary phosphorus, 1.061 Gm.

Roentgenologic Examination.—This also emphasized the unilaterality of the pathologic changes. The skull and spine and bones of the right extremities did not reveal pathologic changes. The left upper extremity showed no changes in the scapula and clavicle, but the left humerus (fig. 2) revealed definite hyperostotic-porotic changes involving almost the entire diaphysis. Only in the distal end and in the upper epiphysis could normal bone structure be seen. There was an almost uniform and equal thickening of the diaphysis. The cortical bone was markedly thinned out and formed only a very thin bony layer, which, however, in no place

Fig. 2.—Roentgenogram showing hyperostotic-porotic changes in the diaphysis of the left humerus. The upper epiphysis and the distal end of the bone show normal structure; the rest of the bone is cloudy and porotic.

was completely interrupted. The surface of the diaphysis was smooth, and there were no signs of active apposition of periosteal bone. The shadow of the bone was cloudy and porotic; only in a few places could a definite structure be seen. These areas probably represented areas of spongy bone where the pathologic changes had not yet appeared. The picture was that of diffuse osteoporosis without cyst formation. In addition to the marked increase in thickness, the diaphysis also showed a distinct increase in length (¾ inch), despite some bowing at the middle third. There were no signs of a recent or healed fracture.

Left Forearm (figs. 3 and 4).—Lesions similar to that of the humerus were seen in the diaphysis of the left radius and in the bones of the thumb. The upper two thirds of the diaphysis of the radius were considerably enlarged and showed the same cloudy and porotic shadow as the humerus. A distinct line of demar-

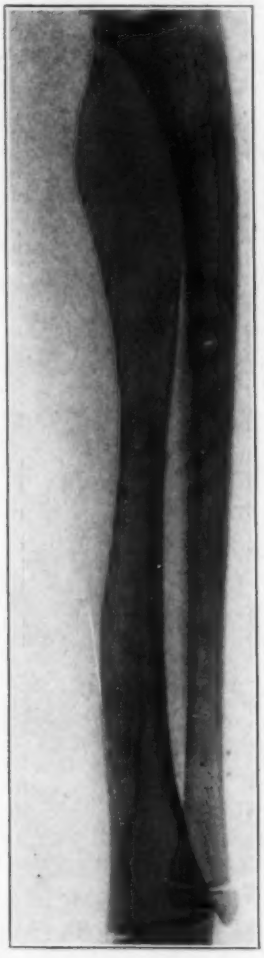

Fig. 3.—Roentgenogram of the left forearm, lateral view. The radius is considerably enlarged in its upper two-thirds; the distal third and the entire ulna are of normal structure.

cation between the middle and lower third separated the diseased from the healthy bone tissue. The epiphyses of the radius and the entire ulna did not show pathologic changes.

The bones of the wrist and of the four fingers were normal. The first metacarpal bone and both phalanges were uniformly and considerably thickened. The cortical bone was thinned out, and the shape was cylindric instead of biconcave. The diaphyses showed the same porotic shadow as the humerus and radius.

Left Lower Extremity.—The left femur (fig. 5) showed marked bowing of its upper end. The bone was thickened in its upper third, and the cortical bone on the outer side of the femur was markedly thinned out. The bone structure was irregular; osteoporotic changes were prevalent. There was an oblique line going

Fig. 4.—Anteroposterior view of the left forearm and hand. Only the radius and the bones of the thumb are involved.

downward and outward from the region of the lesser trochanter, representing probably the old fracture which was completely healed. The upper end of the femur showed the same cloudy shadow as the bones of the upper extremity. The greater trochanter and the proximal epiphysis had evidently been spared; they showed normal, although porotic, bone structure. Marked coxa vara was present; the greater trochanter almost touched the outer edge of the roof of the acetabulum (there were no intrinsic pathologic changes in the hip joint).

The diaphysis was involved in almost its entire length. There were differences in the bone structure at various levels of the femur. The cloudy porotic shadow of the upper portion has already been mentioned. The upper part of the distal fragment showed more irregularities, with areas of more pronounced osteosclerosis. These alternated with extensive areas of osteoporosis which showed

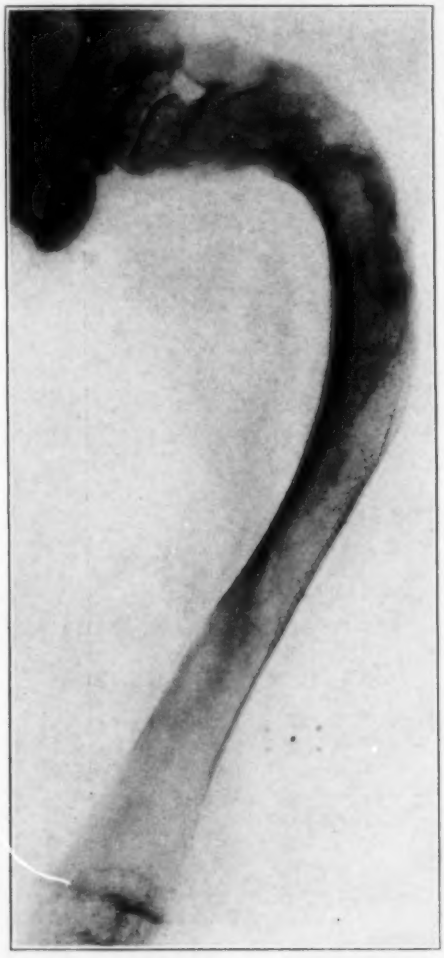

Fig. 5.—Roentgenogram of the markedly deformed left femur with irregular, mainly porotic, structure.

bony trabeculae and were free from the cloudiness seen in the upper fragment. Farther down the changes were almost purely porotic and were combined with slight enlargement of the femoral diaphysis. The distal third of the femur was less porotic, but here also the bony structure was completely changed; the normal spongy bone was replaced by a rather dense spotty and spongy mass which looked almost like cotton. The distal metaphysis and epiphysis showed normal but porotic structures.

The roentgenograms of the leg showed involvement of the tibia only (fig. 6). Almost the entire diaphysis showed the same hyperostotic porotic process which led to an increase of thickness and length (1½ inches [3.8 cm.] in the lateral view), resulting in bowing of the tibia. There was a marked valgus deformity at the junction of the middle and upper thirds. The distal third was involved

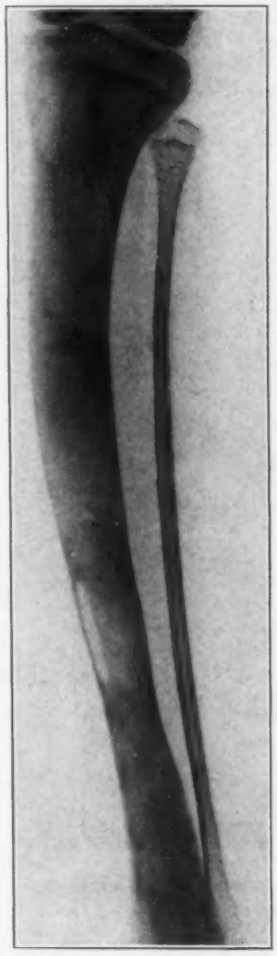

Fig. 6.—Anteroposterior view of the left leg; only the tibia is involved, with an increase in thickness and length.

to a lesser degree and was not enlarged. The cortex, although porotic, still seemed to be the old one. The spongy bone, however, had already been transformed and gave the same picture as the upper portion of the tibia.

The changes in the left foot corresponded to those in the left hand; the bones of the big toe only were involved (fig. 7). There was also some irregularity in

the bony structure of the first cuneiform bone and possibly of the scaphoid, but it was difficult to ascertain whether these changes were due only to atrophy resulting from disuse.

Biopsy.—For further information biopsy was performed (Oct. 27, 1932). A piece of bone was taken from the left tibia at the junction of the middle and lower thirds. Histologic examination revealed the following changes: The cortical bone was much thicker on the distal end of the specimen than on the proximal end; it was composed of rather compact lamellar bone with haversian canals.

Fig. 7.—Anteroposterior view of the left foot, showing involvement of the bones of the big toe, possibly of the scaphoid and first cuneiform bone.

These canals were enlarged by the osteoclastic resorption of bone, forming irregular marrow spaces with hyperemic fibrous bone marrow. The resorption of the old lamellar bone was followed by the formation of small trabeculae of fibrous bone tissue. Near the proximal end the old lamellar cortical bone had almost completely disappeared, and there was only a thin bony layer formed by the apposition of periosteal bone. Inside this layer a rather dense fibrous bone marrow was present, in which many thin trabeculae of primitive fibrous bone were embedded. The central portions were calcified; the superficial layers were osteoid. Near the endosteal surface of the cortex trabeculae of old lamellar bone were still present, which were lacunar in outline. Some of these fragments were

included in the central portion of primitive fibrous bone. The marrow spaces adjacent to the old cortex still showed fatty bone marrow with lamellar spongy bone, but in many places, especially along the vessels of the marrow, the fatty bone marrow had been replaced by fibrous tissue. This led to osteoclastic resorption of the old lamellar bone and to its replacement by fibrous spongy bone. The new spongy bone was without static arrangement. No cartilaginous tissue could be found.

Operation and Recovery.—Because of the histologic observations and roentgenologic findings, osteitis fibrosa von Recklinghausen was considered as a diagnosis, and an exploratory operation was performed on the parathyroid glands (Dr. Petersen, Nov. 23, 1932). No parathyroid tumor was encountered. The two lower parathyroid glands were removed. Histologically, they did not show pathologic changes. The patient made a normal recovery and was discharged for three months. On her return, in March, 1933, her general condition was found to be excellent. There were practically no changes in the local and chemical conditions or in the roentgenologic findings.

COMMENT

The findings in this case suggest that the condition was a systemic disease of the bones which involved the skeletal system unilaterally, but did not involve all the bones of the affected side. The involvement of the bones appears to have followed certain rules, as of the bones of the upper extremity only the humerus, radius and the bones of the thumb were affected. The left lower extremity showed in a similar way involvement of the femur, tibia and great toe. There was distinct asymmetry of the face, owing to underdevelopment of the left side. The unilateral aspect of the disease and the asymmetry of the face are more or less characteristic symptoms of Ollier's achondroplasia.

Ollier,[1] in 1899, described a definite disease of the bones characterized on roentgen examination by irregularity and delay of endochondral ossification. The epiphyseal cartilage does not undergo normal ossification, but preserves its structure and remains in the form of irregular cartilaginous masses which commonly require a long time to become ossified. These masses may be superficial or deep, subperiosteal or intramedullary. The phalanges of the toes, and especially those of the fingers, are sites of predilection. A part of the phalanx or the whole thickness may be involved. Ollier mentioned disseminated chondromas of the phalanges. In the long bones of the extremities near the epiphyseal plate osteochondromatous tumors are also found. They transform the juxta-epiphyseal portions into transparent, distended, voluminous masses. The epiphyses remain more cartilaginous and show less bone tissue than in normal persons. Ollier assumes that dyschondroplasia takes place on both sides of the epiphyseal plate. The irregularity of

1. Quoted by Frangenheim.[2]

ossification leads to a disturbance in length growth and in deformities. Ollier did not doubt the cartilaginous nature of the lesion, although he made no histologic examination.

Wittek,[1] in 1906, published a monograph on dyschondroplasia, with the report of one case. He concluded:

> There is a congenital lesion of the cartilage of the epiphyseal disc consisting in a primary growth disturbance. As far as the long bones are concerned, this lesion is strictly unilateral. The first clinical symptoms become manifest in early childhood and lead to shortening of the extremity with tumor formation of the long bones at the epiphyseal plates. The tumors are chondromata; they consume during growth cartilaginous material which under physiological conditions would be used for length growth. The proliferation of cartilage occurs very irregularly in all directions, possibly the most in the direction of least resistance. The process leaves its strict unilaterality only at the distal ends of the extremities where it also changes its appearance. Here, the cartilaginous masses do not arise from the epiphyseal plate only but also from isolated particles of it. The disease is a characteristic symptom-complex and occupies a distinct position among the group of multiple chondromata.

Therefore, Wittek agreed with Ollier in considering the condition as a disease *sui generis*.

Frangenheim,[2] in 1911, and Hackenbroch,[3] in 1922, rejected the views held by Ollier and Wittek and considered dyschondroplasia in all cases as multiple chondromas. Frangenheim especially stated that he would perhaps consider dyschondroplasia as a new disease if there were really strict unilaterality. But in no case did he find the unilaterality persistent.

In the years following, many articles on Ollier's disease were written, and the number of unilateral cases reported in the literature amounts to about thirty. Some of these do not fulfil completely Fragenheim's postulates, but there are a number of cases of the strictly unilateral type. Thus there is no doubt of the existence of a unilateral disease of cartilaginous dystrophy (Ollier's disease) which histologically and roentgenologically is in intimate relationship with the group of multiple chondromas.

If one tries to place the case reported in this article in the category of Ollier's achondroplasia one meets with some difficulties. Apart from the unilaterality and the asymmetry of the face (a frequent but by no means constant symptom in Ollier's disease), there are a number of differences between this case and those reported in the literature.

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2. Frangenheim, P.: Chondromatose des Skeletts, Beitr. z. klin. Chir. **73**: 226, 1911.

3. Hackenbroch, M.: Ollier'sche Wachstumsstörung: Chondromatose des Skeletts, Arch. f. orthop. Chir. **21**:206, 1922; Ueber Ollier'sche Wachstumsstörung und Chondromatose des Skeletts, Fortschr. a. d. Geb. d. Röntgenstrahlen **30**:432, 1922-1923.

In Ollier's disease the clinical signs become noticeable within the first year of life or soon after the child walks. The first sign is usually deformity of the extremities combined with shortening. My patient was, according to her mother, perfectly well until her fifth year. At that time she began to limp and soon after sustained a pathologic fracture. The fracture healed slowly, with marked deformity, and since that time the patient had shown progressive changes in the bones. It is possible that changes in the bones were present before the clinical signs were manifest, but this is only a supposition, and it is doubtful whether the disease started very long before the clinical signs appeared.

Another outstanding feature of Ollier's disease is shortening of the affected extremities. This is not only an apparent shortening caused by deformities but a real one and is due to an intrinsic disturbance of the endochondral ossification. My patient showed shortening of the left lower extremity, but this was only apparent owing to the deformity caused by the fracture. The tibia and humerus, however, showed a definite increase in length, so that the tibia, which was fastened at both ends to a perfectly normal fibula, showed marked anterior bowing.

Furthermore, there are marked differences between the roentgenograms of my patient and those of patients with Ollier's disease. Ollier's disease resembles roentgenologically enchondromatosis of the skeleton. A coarse structure is seen in the region of the metaphyses, with irregular strands, enlarged areas of rarefaction, through which a few long bony trabeculae run. The rarefied areas represent clear spaces which frequently contain small dense nodular shadows; these are often conglomerate. The affected metaphyses usually show a clublike enlargement, with thinning of, and even defect in, the cortex. Practically all investigators agree that the transparent irregular masses are formed in the metaphyses. Flotow [4] stated that he was almost always able to find in the roentgenograms a bridgelike formation running from the epiphyseal plate toward the chondromatous metaphyses. In long bones in which there is involvement of both metaphyses, the central portion of the diaphyses often shows normal bone tissue. The changes in the epiphyses are less marked; deformities and delaying ossification, however, are frequently described.

The most striking feature in the roentgenograms in my case is that the pathologic changes occurred only in the diaphyses; the epiphyses and the epiphyseal plates were apparently not involved in the process. The metaphyses may or may not have shown pathologic bone structure. One does not get the impression that the process started primarily in the metaphyses or directly in the epiphyseal plate. In these respects

4. Flotow, F.: Ueber den Halbseitentyp der Chondromatose, Ztschr. f. orthop. Chir. **51**:505, 1929.

this case differs from one of Ollier's disease, and even more so in regard to the bone structure and the configuration of the involved diaphyses. The clublike enlargement by a transparent irregularly nodular tumor mass was not present, but there was a more diffuse widening of the diaphysis, with a cloudy porotic osseous shadow. There were no circumscribed areas of rarefaction or small spotty, dense shadows of calcification. There was no "blowing up" of the cortex with defect, but the cortex, which was in most places extremely porotic, was rather straight and preserved its continuity.

Finally, the biopsy in this case gave a histologic picture which is quite unlike that of Ollier's disease. All the investigators who performed biopsy in cases of Ollier's disease reported enchondroma and mature hyaline cartilaginous tissue with or without calcification. The specimen removed from the left tibia of my patient, at the level separating the diseased from the normal bone, showed the typical picture of osteitis fibrosa.

Thus the clinical and roentgenologic findings and histologic observations speak against the diagnosis of Ollier's disease. The most important fact is the histologic observation which points toward the diagnosis of osteitis fibrosa. Before further discussion of the relationship to Ollier's disease, the significance of the histologic diagnosis of osteitis fibrosa in this case must be considered.

It is necessary, however, to emphasize that the histologic picture of osteitis fibrosa has no specific significance. Histologically, one can have the identical picture in Recklinghausen's disease, in osteitis fibrosa localisata, even in some areas in Paget's disease, in osteomalacia and rickets, in chronic inflammatory diseases of the bone marrow, in cases of fracture with callus formation and in other conditions. Therefore, one must admit that a diagnosis based only on histologic examination of a relatively small piece of bone is usually insufficient and may lead to great error. Unlike examination of the parenchymatous organs, a single slide in diseases of the bones may disguise more than it reveals. In diseases of the bones histologic examination can be of value only if different bones on many sections have been carefully examined.

On this basis the osteitis fibrosa in the case reported might possibly be interpreted as an accidental finding, a form of reaction of the bone marrow to a lesion of another type not contained in the specimen. It is theoretically possible that the bone marrow near a chondroma may show fibrosis, with new bone formation, and so a final diagnosis of osteitis fibrosa would be inadequate and misleading. But I do not think that such skepticism would be justified in this case. The biopsy specimen was taken at a level where roentgenologically healthy bone tissue was invaded by the pathologic process. The diseased portion showed, however, the same irregular cloudy and porotic shadow seen in all the other

affected bones. There is no doubt that this shadow corresponds to the dense substantia spongiosa of tiny bony trabeculae composed of fibrous bone which is only partially calcified. The combined study of the biopsy specimen and the roentgenograms makes the diagnosis of osteitis fibrosa more definite, and it may almost be taken for granted that most of the long bones of the left side were affected by fibrous osteodystrophia.

The question arises whether this condition is one of the common forms of osteitis fibrosa. When the patient was first admitted to the hospital the diagnosis was osteitis fibrosa localisata of the upper end of the femur, with pathologic fracture. Unfortunately, roentgenograms of the pelvis only were taken, so that nothing can be said about the condition of the other bones at that time. But, as the literature contains no reference to circumscribed osteitis fibrosa which changed into a multiple or generalized form, and as it becomes more and more the general opinion that localized and generalized forms of osteitis fibrosa are essentially different diseases (with common histologic signs), I should be inclined to think that in my case the condition began primarily as a multiple osseous lesion. For mechanical reasons, however, the changes in the lower extremities, especially in the femur, became clinically manifest sooner.

Whether the condition in my case began primarily as a localized or multiple osseous lesion, osteitis fibrosa localisata can be ruled out. But is the multiplicity of osseous lesions a sign of a generalized form of disease of the bones, or, in other words, does this case represent a rare form of Recklinghausen's disease with disease of the bones on one side of the body only, just as Ollier's disease represents a rare form of enchondromatosis?

I do not think so. Recklinghausen's osteitis fibrosa is a generalized disease of the bones, with an endocrine disorder as the central cause, and therefore it must affect all the bones of the skeleton. There may be degree of involvement of the different bones, for mechanical reasons, but histologically all the bones show characteristic changes. A central endocrine disorder is incompatible with disease of the bones of one side only. Aside from the fact that Recklinghausen's disease is extremely rare in the first decade of life, it gives a rather characteristic roentgenogram, the typical signs of which are porosis and cyst formation. There is no hyperostosis. If hyperostotic changes with periosteal bone production are found, they occur only at the site of pathologic fractures and are not marked. In my case the affected bones showed marked osteoporosis, but in combination with hyperostotic changes; thickening of the bones was an outstanding feature. The porotic changes were diffuse and apparently did not lead to cyst formation.

Finally, the chemical findings and the normal condition of the parathyroid glands speak against Recklinghausen's disease. In this disease

it is almost the rule to find a high content of serum calcium and a high output of calcium in the urine, and a tumor of one or more of the parathyroid glands is frequently, if not always, encountered. In my case nothing remarkable could be found in the blood (the increase of phosphatase may be due, as in Paget's disease, to the intensive new bone production rather than to the resorption of old normal bone), and the phosphorus and calcium content of the urine were likewise essentially negative. So far as the parathyroid glands are concerned, no tumor could be seen at the time of operation, and the two glands which were removed appeared normal histologically.

So one may exclude Ollier's achondroplasia and the more common forms of fibrous osteitis, despite the fact that in this case there are certain features common to both these diseases. Judging from the cases reported in the literature, the condition represents a unique bony lesion for which the term "osteodystrophia fibrosa unilateralis" seems the most apt. The singularity of this condition is illustrated by the roentgenologic picture, which showed essentially identical pathologic changes in all the affected bones.

But it may be that the pure case of osteodystrophia fibrosa unilateralis represents only an extreme type in a line on the opposite end of which is the pure case of Ollier's achondroplasia.

There are findings in the roentgenograms in cases reported in the literature suggesting this possibility. Orator,[5] in 1925, reported the case of a man, aged 23, with multiple enchondromas on both hands. Biopsy showed atypical chondroma. Moreover, the diaphysis of one humerus showed bending combined with a peculiar enlargement of the bone. The cortex was atrophic, and there were several longitudinal strips of more marked porosis. Orator found similar and even more marked changes in a girl, aged 15, with a disturbance of growth enchondromatosis and multiple cartilaginous exostoses. He believed that in these two cases there was a disturbance of bone formation on the basis of cartilaginous as well as of fibrous periosteal changes. In this way chondromatosis and osteitis fibrosa would represent analogous bone diseases, the first due to disturbance of the endochondral, the latter to disturbance of the periosteal, bone formation.

In this connection it is also of interest to quote Cole[6] in his article on chondrodysplasia. He wrote that many roentgenograms of patients with proved osteitis fibrosa show a condition in the bone which resembles closely that seen in some of the reported cases of chondrodysplasia. A definite classification of cartilaginous dystrophies is still impossible.

5. Orator, V.: Ueber Mischformen von Skelettchondromatose und Ostitis fibrosa, Arch. f. klin. Chir. **134**:813, 1925.

6. Cole, W. H.: Chondrodysplasia, Surg., Gynec. & Obst. **42**:359, 1926.

The possibility that the widely different findings in some of these cases are only manifestations of different stages of the same condition must be seriously considered.

The roentgenograms illustrating the articles dealing with dyschondroplasia (as many as our investigation permitted) showed only in one case that the combination of dyschondroplasia and osteitis fibrosa might be present. This occurred in the case of a 19 year old girl reported by Dotti in 1930.[7] There were typical enchondromatous changes in the right forearm and right hand. No other bony lesion could be found, except in the diaphysis of the right humerus, which appeared to be blown up, with zones of osteoporosis and enlargement of the medullary cavity. Both epiphyses appeared to be normal. I assume from the description and from the illustration that the lesion in the humerus is more likely one of osteitis fibrosa than of dyschondroplasia.

All these observations show that there are mixed forms of osteitis fibrosa and dyschondroplasia, although in none of the cases mentioned was the diagnosis of osteitis fibrosa proved histologically. In the light of these findings, it seems justifiable to place my case of osteodystrophia fibrosa unilateralis on one end of a straight line at the opposite end of which is Ollier's achondroplasia as a strictly unilateral skeletal lesion. By this, however, I do not mean that the differences in the clinical findings and in the roentgenograms are only signs of different stages of the same condition, as one might believe with Cole. Practically nothing is known about the etiology of these diseases of the bones; but even though the etiology were the same for both forms, the pathogenesis is certainly different. I have already mentioned the main differences between Ollier's chondrodystrophia and osteodystrophia fibrosa unilateralis. The first is a primary lesion of the cartilage of the epiphyseal plate and therefore involves essentially the metaphyseal region. Osteodystrophia fibrosa unilateralis is apparently a diaphyseal lesion exclusively. The process of endochondral ossification goes on within normal limits and leads to a normal primary substantia spongiosa, even in metaphyses which in greater part are already involved in the process and therefore appear in the roentgenogram with cloudy porotic shadows. Shortening of the bones is not a characteristic feature of the disease. It seems even more evident that the process is inclined to lead rather to lengthening of the bones, possibly as a result of the marked hyperemia of the bone marrow.

As with the endochondral ossification which apparently resulted in this case in normal primary substantia spongiosa, one gets the impression that the periosteal bone formation also is not the primary seat of patho-

7. Dotti, E.: Contributo alla conoscenza del morbo di Ollier, Chir. d. org. di movimento **15**:476, 1931.

logic changes. Such changes seem to become manifest with the so-called internal molding resorption which removes the primary spongy and cortical bone, replacing it in normal cases with mature lamellar bone with static arrangement. In the affected bones in my case, however, the internal molding resorption, instead of leading to the formation of lamellar bone, for some unknown reason produced fibrous bone marrow with a fibrous spongy bone.

If one asks the cause of this peculiar osseous lesion one finds no satisfactory answer. One must supplant one's deficient knowledge by more or less vague hypotheses, as, for instance, a lesion of the mesoblast at an early stage of embryonic life, possibly just after the ovum divides into two blastomeres. On the assumption that the plane of first division corresponds to the median sagittal plane of the body, a lesion of one of the blastomeres could explain the strict unilaterality of the bone lesion.

Of greater interest, because it is based on facts, is Bentzon's[8] explanation of Ollier's disease on the basis of anomalies arising in the vegetative nervous system. Bentzon observed a case of Ollier's disease in which two peculiarities interested him most. One was the characteristic regular localization of the cartilaginous stripes in the affected bone, and the second the pronounced tendency to hemilaterality. Bentzon thought that the pathologic changes of the bones in Ollier's disease follow paths similar to those of the arteries and nerves of the bones. The tendency toward unilaterality suggests dependence on the nervous system, especially the sympathetic cord.

On the basis of this hypothesis, Bentzon experimented on young rabbits by injecting absolute alcohol in an attempt to influence the sympathetic cord. A series of roentgenograms was taken. In all the animals but one the results were negative. In the rabbit which showed positive results, gross osseous changes were found in the first phalanx of the second toe of the forepaw one month after the operation. The anomalies showed a striking similarity to those found in Ollier's disease. If the changes in the rabbit's toe are compared with those in the thumb and great toe of my patient, they are found to be almost identical. Bentzon's findings seem to correspond more to the findings in my case than to any reported in the literature. Unfortunately, the rabbit was not killed until five months later. During this time the changes in the bones decreased considerably. Microscopically, the affected bone showed enlargement of the marrow cavity and a coarse cortical structure of a more osteoid type. There was no trace of cartilage. Bentzon supposed that it had vanished and turned into osseous tissue before microscopic examinations were made.

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8. Bentzon, P. G. K.: Roentgenologic and Experimental Studies on the Pathogenesis of Dyschondroplasia (Ollier's Disease), Acta radiol. **3**:89, 1924.

Bentzon concluded from his experiments that Ollier's disease represents the typical reaction of the bones to certain disorders in the innervation of the blood vessels, but he did not try to explain the etiology of the disease. He presumed that congenital aplasia of the nervous elements was present in the early and more serious cases. That Ollier's disease does not affect all the bones of one extremity is due, according to him, to an irregular distribution of the peripheral ganglions which in some places regulate the innervation of the vessels when central regulation fails. The disturbance in regulation leads to an increased circulation of blood, thus giving rise to pathologic processes in the bone similar to callus formation.

By his experiments, Bentzon showed clearly that changes similar to those in Ollier's disease may be due to a disturbance in the innervation of the vessels. Jansen,[9] however, pointed out that the shortening of the affected extremities, as commonly found in Ollier's disease, is not compatible with Bentzon's supposition of abnormal active hyperemia. Jansen thought that the latter condition can bring about only gigantism or cavernous angiomas. I also believe that Bentzon's experiments do not throw much light on the pathogenesis of Ollier's disease (which they were intended to explain), but consider his findings extremely important in explaining the development of the pathologic changes in my case of osteodystrophia fibrosa unilateralis. I have already mentioned the striking similarity between the anomalies in the rabbit and those of the thumb and the great toe in my patient. Also, Bentzon's histologic observations, with the lack of cartilaginous tissue and the osteoid type of the cortical bone, would suggest fibrous osteodystrophia rather than dyschondroplasia. Another factor is that the bone marrow in my case was hyperemic and well vascularized, and, last but not least, almost all the affected bones in the patient were longer than normal.

So I believe that I am justified in applying Bentzon's conclusion from his experiments to my case. On the basis of Bentzon's work, osteodystrophia fibrosa unilateralis must be considered as a typical reaction of the bones to active hyperemia of the bone tissue. The hyperemia is due to anomalies in the vegetative nervous system, followed by paresis of the muscles of the vessels, with vascular dilatation.

The evident similarity, however, between osteodystrophia fibrosa unilateralis and Ollier's achondroplasia (especially the asymmetry of the face and the unilaterality of the disease) points to a common cause, despite the essential differences already mentioned. I assume that the common cause is an anomaly of the sympathetic nervous system. If this anomaly is followed by vascular dilatation, fibrous osteodystrophia

9. Jansen, Murk: Ueber Dissoziation der Wachstumsprozesse in Knochen, Verhandl. deutsch. orthop. Gesellsch. **49**:274, 1927.

may arise; if, however, it is followed by vascular constriction, a disturbance in growth similar to Ollier's disease may occur.

Another series of experiments undertaken by Bentzon might speak in favor of this supposition: Alcohol was injected into young rabbits around the nutrient artery of the leg. By roentgenograms it was shown that in animals in which the artery had been reached structural changes in the bone were present, besides periosteal deposits at the site of injection. The changes in the bone resembled those in Ollier's disease, but as a rule they disappeared quickly, persisting for only about one week. But in two rabbits the changes lasted longer and were clearly cartilaginous. It seems likely that the periosteal and parosteal reaction following the injection of alcohol causes constriction rather than dilatation of the vessels. Therefore, I think that the cartilage formation in the diaphysis may be due to a decrease in the afflux of blood rather than to an increase, but this is only a supposition. It is certain, however, that Bentzon's experimental work should be repeated on a much larger basis.

EXAMINATION OF TUBULAR ORGANS AND ARTERIAL SYSTEMS OF RABBITS BY FILTERED ULTRAVIOLET RADIATION

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We have shown that a dye such as eosin or mercurochrome when injected either intravenously or intravesicularly will visualize the gallbladder and extrahepatic biliary ducts in the opened abdomen of rabbits when they are exposed to filtered ultraviolet radiation.[1] In our work the source of ultraviolet radiation was a mercury vapor arc lamp with a nickel oxide filter. The filter permits the selection of waves ranging from 300 to 400 millimicrons in length (with the greatest spectral intensity at 366 millimicrons). Tissues or fluorescent dyes when examined by filtered ultraviolet radiation emit secondary visible rays; this phenomenon is called fluorescence.[2] In the aforementioned investigation we found that the dye, which fluoresces as a golden color, can be seen progressing from the gallbladder to the duodenum, and then farther down the intestinal tract (figs. 1 and 2). Obstruction of either the biliary or the intestinal tract can be demonstrated by the arrest of flow of the fluorescent fluid. It would seem that the use of this procedure may have application in the various fields of experimental surgery in animals.

In pursuing the work further, we found that intragastric administration of the dye in rabbits produces only slight visualization of the gallbladder and of the extrahepatic biliary ducts. We have been able to convince ourselves that the fluorescence of the gallbladder and the ducts is due to their content of dye and not to any vascular coloring in the serosa. (It is important to note that the degree of fluorescence

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Dr. H. L. Jaffe aided us in this work.

From the Laboratory Division of the Hospital for Joint Diseases.

Aided by a grant from the Emanuel Libman Fellowship Fund in Memory of Adele Schiff.

1. Sutro, C. J., and Burman, M. S.: Visualization of the Biliary System by Fluorescence, J. A. M. A. **99**:2024 (Dec. 10) 1932. Fabre, R.: Beitrag zum Studium der Anwendung der Fluorescenzerscheinungen in der biologischen Chemie, Bull. Soc. chim. biol. **7**:1024, 1925.

2. Sutro, C. J., and Burman, M. S.: Examination of Pathologic Tissue by Filtered Ultraviolet Radiation, Arch. Path. **16**:346 (Sept.) 1933; Fluorescence of Cartilage Exposed to Filtered Ultraviolet Radiation, Arch. Path. **15**:537 (April) 1933.

depends on the thickness of the wall of the organ, and that a thick wall will prevent the penetration of ultraviolet light.) To exclude a vascular factor in an anesthetized rabbit, a segment of the small intestine 2 inches (5 cm.) distal to the termination of the duodenum was made avascular by tying off its blood supply; the isolated segment of intestine was clamped off at each end. When this was done, an intravenous injection of eosin or mercurochrome did not reveal the presence of the dye in the isolated loop of intestine under filtered ultraviolet radiation. When the upper or proximal clamp was released, the dye, obstructed artificially in its downward progress from the extrahepatic ducts, gradually entered

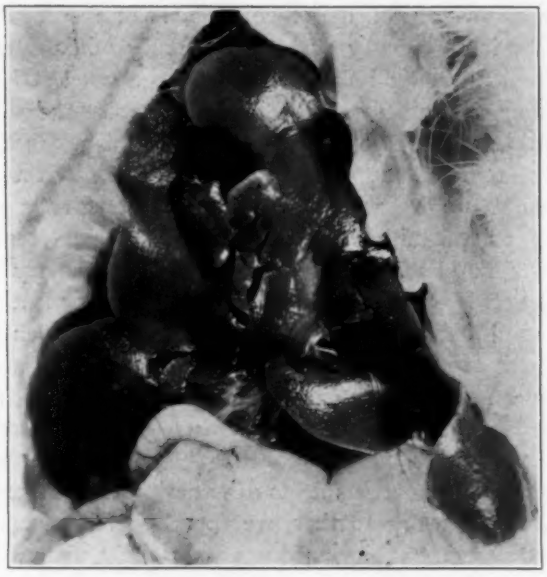

Fig. 1.—The liver, gallbladder, stomach and duodenum of a rabbit.

the avascular segment. Coincident with this procedure, in the same animal, a segment of small intestine 2 inches proximal to the ileocecal junction was constricted by clamps at each end, care being taken to preserve its blood supply. Slight fluorescence was noted, with slight coloration of the mesenteric vessels supplying this and other portions of the intestine. These results would seem to indicate that most of the dye reaches the small intestine by way of the extrahepatic biliary ducts rather than by way of the blood stream.

VISUALIZATION OF OTHER TUBULAR ORGANS

A study of the fluorescence of other tubular organs of the rabbit was made after the direct injection of the dye into the lumens.

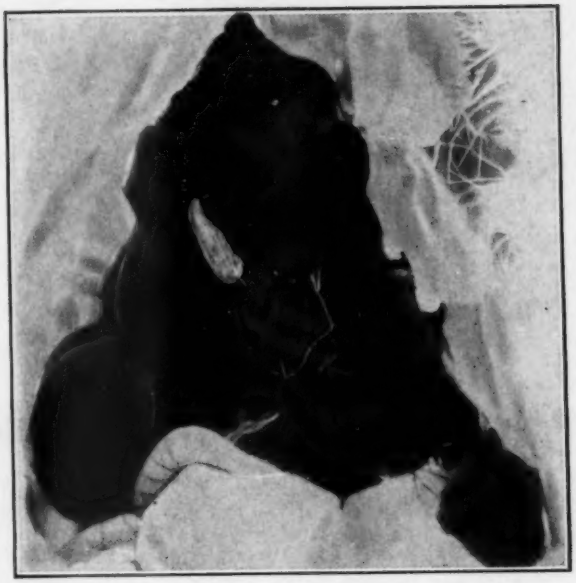

Fig. 2.—Gallbladder, extrahepatic biliary ducts and duodenum on examination with filtered ultraviolet radiation after the intravenous injection of 2 per cent mercurochrome.

Female Genital Tract.—Enough of a 2 per cent solution of aqueous eosin was injected into the bicornate uterus of a living rabbit to distend it. With slight pressure, the dye passed over into the fallopian tubes. Under filtered ultraviolet radiation the uterus and tubes were golden yellow. During the injection some of the dye spilled over into the abdominal cavity through the fimbriated ends of the tubes, producing a visual Rubin test. The ease with which the tubes fluoresced in the rabbit suggested the investigation of the genital system of man. Injections were made through the rigid external os of the cervix into the genital system of a girl, aged 14, obtained at autopsy. On incision, the uterus showed intense staining of the endometrium with deep penetration of the dye into the muscular coat. When watery eosin was injected into the lumen of the fallopian tube at the uterotubal junction, a strong golden fluorescence of the tube was noted, and with the increased pressure of the injection at the junction, the dye diffused throughout the broad ligament, so that it became a golden sheet. It is well known that a thick-walled tube will not be effectively visualized; however, if the dye reaches the tubal lumen it will be possible to observe the emission or nonemission of the dye from the fimbriated end. An attempt is being made to produce a nontoxic fluorescent iodized poppy-seed oil. This will enable the visualization under fluorescence of what the radiograph demonstrates, provided the fallopian tubes are not thickened.[3]

Urinary Tract.—When a 2 per cent solution of aqueous eosin was injected into the lumen of a ureter of a living or dead rabbit (downward toward the bladder), a fine stream of dye passed through the ureteral orifice; on irradiation of the opened urinary bladder, a fine golden stream of dye was seen, and the ureteral orifices were stained a golden yellow. When the dye was injected toward the pelvis of the kidney (pyelovenous backflow), the pelvis was filled if enough dye was used; with sufficient pressure, rupture through the calices into the kidney substance occurred.[4]

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3. It may be noted that Hauser (Strahlentherapie **33**:582, 1929) observed a red fluorescence in all forms of vaginal hemorrhage, whether normal, as in menstruation, or abnormal. This is the only reference we can find on the use of filtered ultraviolet light in gynecology.

4. Hadjioloff and Kresteff (Compt. rend. Soc. de biol. **106**:662, 1931) studied the fluorescence of urine in higher and lower vertebrates. They believed that the yellow fluorescence of urine is due either to urochrome or to urobilin, though the problem may be complicated by the presence of microbic and ferment factors. The intensity and color of urine apparently vary with the species. Truc (Compt. rend. Soc. de biol. **99**:1847, 1928) devised a fluorescent method of testing renal permeability by the injection of a 0.5 per cent solution of acriflavine hydrochloride in animals; the solution is excreted by the kidneys within thirty minutes and fluoresces a yellow-green. The substance, it is noted, is eliminated unequally by the urinary tubules and is not shown in the glomeruli. In man, the dye appears in the urine first within fifteen minutes after injection and remains there for thirty-six hours. The p_H of the urine has no bearing on the fluorescent reaction.

The ureter showed only a golden fluorescence when distended with aqueous eosin.

Bronchial Tree.—The direct injection of a 2 per cent watery solution of eosin into the trachea of a dead rabbit caused a visualization of the trachea and its branches, down to the very finest terminal bronchioles; it was noted, however, that the injection of the finer bronchioles was irregular, mucous plugs apparently blocking the further passage of the dye. The uncut surface of the lung showed golden, triangular, infarct-like areas, corresponding to the segments in which patent bronchioles allowed the passage of the dye. A fluorescent iodized poppy-seed oil would be of great aid in the visualization of the bronchi and the alveoli in the opened thorax by means of filtered ultraviolet radiation.

Esophagus.—Direct injection of a 2 per cent solution of aqueous eosin into the esophagus of a dead rabbit gave excellent fluorescence of that organ, especially when it was temporarily clamped off at its gastric end.

VISUALIZATION OF THE ARTERIAL TREE

After investigating the visualization by filtered ultraviolet radiation of tubular and hollow organs in the rabbit following the intravenous or direct injection of eosin or mercurochrome, it was decided to study the visualization of the arterial tree in the same animal.

The injection by a syringe of 50 cc. of a 2 per cent watery solution of eosin or mercurochrome into the abdominal aorta of a dead rabbit which had been exsanguinated before death disseminated the dye widely through the vascular channels of the body. Under the action of filtered ultraviolet radiation, which with eosin or mercurochrome produces a strong, golden-yellow fluorescence, the entire arterial system was delineated, as if dissected in gold. The actual outlining of the course of the vessels under this radiation permitted much easier dissection than with the naked eye. The venous channels were not colored, and the veins fluoresced a dark brown because of their large content of clotted blood. Examination of the vascular tree should be conducted at once, since the dye diffuses into the adjacent tissues. During the course of the injection, the gastric, mesenteric, intestinal and splenic arteries were observed with the naked eye to color, but under radiation the vessels fluoresced a rich golden yellow, which extended to the finest ramifications. The use of a hand lens enabled more detailed study.

The coronary arteries of the heart of a rabbit which had received injections were well outlined, and some vessels in the endocardium were visible. The myocardium showed no vessels. The parietal pericardial vessels were also stained. The kidneys showed pin-point vascular markings in the cortex; the medulla was at first free from fluorescence but

became fluorescent later by diffusion. The ureter could be traced by the fluorescence of the periureteric vessels. The urinary bladder showed fine vascular markings in its mucosa. In the dead animal, after an intra-aortic injection of the dye, the gallbladder and the extrahepatic vessels showed up well. The vascular outlines of the mesenteric, intestinal, gastric and splenic arteries, especially the finer serous ramifications of the former, were as stated earlier, well defined. Diffusion took place rapidly in the serosa of the stomach and intestine. The serous vessels about the fallopian tubes were diffusely injected, so that they appeared as golden yellow tubes. The dura of the brain and spinal cord, as well as the arachnoid layer, showed marked diffuse injection, though the cortex of the brain and the substance of the spinal cord did not stain.[5]

Subcutaneous vessels showed diffusely through the unopened skin in many areas. The intercostal vessels in the opened thorax could be fully traced. The major and minor vessels in the arteriovascular tree of the upper and lower extremities could be distinctly followed. Thus, about the knee joint, the median superior geniculate artery was easily seen. The infrapatellar fat and the synovia were also stained golden. The muscular and periosteal vessels were visible. Neither marrow nor cartilage fluoresced a golden color, in either the living or the dead animal. If the dye was injected directly into the bone marrow of a dead animal, the dye could not be demonstrated, owing to the diffuse, dark appearance of hemoglobin. Prolonged soaking of the marrow in the eosin ultimately colored it.

This method may be used for demonstrating the arteriovascular system in part or as a whole, though it is to be remembered that the distinct outline of the finer vessels is lost by diffusion within an hour after injection. Eosin in liquid petrolatum or eosinated beeswax [6] may be used in more permanent preparations. Fixation of a particular region may be accomplished by the use of a 2 per cent solution of eosin in a 10 per cent solution of formaldehyde (4 per cent solution of formalde-

5. Study of the literature indicates that some attention has been paid to the fluorescence of cerebrospinal fluid. Thus Exner (Psychiat.-neurol. Wchnschr. **32:** 218, 1930), who noted that normal spinal fluid fluoresces a deep violet under ultraviolet radiation, studied the alterations of the fluorescence of the fluid in nervous diseases. Schaltenbrand and Putnam (Deutsche Ztschr. f. Nerven. **96:**123, 1927), in an excellent study of the circulation of the cerebrospinal fluid, noted that a 10 per cent solution of fluorescein injected into the blood stream in live animals is demonstrated in the cerebrospinal fluid within fifteen minutes. They did not use filtered ultraviolet radiation in their study.

6. Eosin in liquid petrolatum or beeswax may be prepared by the use of a common solvent, such as cedar oil or xylol, with incubation of the solution for from about thirty to sixty minutes, to insure an even spread of the dye in the petrolatum or beeswax.

hyde U. S. P.). We are uncertain just how long the fluorescence of the finer vessels will last by the latter two methods.

In the living animal, however, the arteriovascular tree was visualized after intra-aortic injection of larger doses of eosin. The dye was excreted by the biliary system and the kidneys, although if large amounts were injected the mesenteric and intestinal vessels showed the dye. The vascular tree of the extremities in a living animal may be visualized by this method if the arterial and venous circulations are retarded temporarily by a tourniquet. When the dye was injected into the beating heart, no particular fluorescence of the heart or the coronary vessels occurred. When the dye was injected into the inferior vena cava of a living animal under pressure in the direction of the liver, a retrograde flow of blood was accomplished, and under sufficient pressure the surface and substance of the liver became finely lobulated by dye markings. Under the radiation the borders of these lobules were outlined in gold. When a frozen section was made of a piece of liver eosin was found both in the central and in the interlobular veins. With release of pressure, the flow of blood became normal again, and the dye was propelled toward the heart. A sample of blood withdrawn from the inferior vena cava gave the characteristic golden color, though the inferior vena cava itself did not fluoresce golden but brown.

No dye was noted in the anterior chamber of the eye after the death of the animal. Other body fluids were not tested.[7]

Modifications and variants of this method could be tried. Thus, for instance, certain phases of placental relations could be investigated in both living and dead animals. The method may be useful in the study of the lymphatic system, since many dyes are transported by the lymphatics. It may also be used to detect minute quantities of dyes in

7. Ehrlich (quoted by Kramer, in Virchows Arch. f. path. Anat. **274**:215, 1930) noted that fluorescein, which is the mother substance of eosin and mercurochrome, is distributed in the body fluids and is not taken up by fat or brain tissue. Schaltenbrand and Putnam noted the extensive distribution of 10 per cent solution of fluorescein, injected into the blood stream, in the skin, mucosae, muscle, connective tissue and dura mater and in various secretions such as the fluid of the anterior chamber of the eye and the cerebrospinal fluid. They pointed out that the substance of the central nervous system is not affected and that no change is noted in vessels, either in the wall or in the lumen. The oral administration of eosin (Rost, quoted by Kramer) gave no local or general effects. Kramer and Tappeiner (quoted also by Kramer) studied the effects of subcutaneous injections of eosin in animals. Tappeiner also injected the dye intravenously. Binet and Fabre (J. de pharm. et chim. **9**:16, 1929) injected olive oil, rendered fluorescent by the addition of *di*-phenylanthracene, into the blood stream and studied the distribution of this fluorescent oil in various organs. The lung is noted as having the greatest lipopexic powers. *Di*-phenylanthracene fluoresces blue and was demonstrated in various proportions in the blood from different organs and tissues.

cavities and fluids of the body. Fluorescent dyes which are so diluted that they are imperceptible by unaided vision are easily detected by filtered ultraviolet radiation.

SUMMARY

A method for the examination of tubular organs by the injection of aqueous eosin or medicinal mercurochrome is proposed. With the use of filtered ultraviolet radiation, many of the tubular organs fluoresce a golden yellow. Similarly, the injection of aqueous eosin or medicinal mercurochrome into the aorta of a dead animal shows the arterial system as golden tubes on examination with ultraviolet radiation.

SPINA BIFIDA AND CRANIUM BIFIDUM

A STUDY OF ONE HUNDRED AND THREE CASES

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INTRODUCTION

The problem of spina bifida has occupied the attention of surgeons for many years, and, in spite of a voluminous literature that has accumulated on the subject, fundamental differences of opinion still exist. Excellent contributions on the anatomy of spina bifida have been made by von Recklinghausen.[1] Keiller [2] and others;[3] however, the underlying factors in the pathogenesis of this condition have not been determined. Many theories have been advanced, but convincing proof of any of them is still lacking. One of us (E. S.) has always felt that hyperactivity of the choroid plexuses in utero before the neural arches have completely closed was a probable cause of the condition. The fact that the choroid plexuses are formed, according to Hochstetter,[4] before the

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1. von Recklinghausen, F.: Untersuchungen über die Spina Bifida, Virchows Arch. f. path. Anat. **105**:243, 1886.

2. Keiller, V. H.: A Contribution to the Anatomy of Spina Bifida, Brain **45**:31, 1922.

3. Tourneux and Martin: L'histoire du spina bifida, J. de l'anat. et physiol. **17**:1, 1884. Fischel, A.: Ueber Anomalien des zentralen Nervensystems bei jungen menschlichen Embryonen, Beitr. z. path. Anat. u. z. allg. Path. **41**:536, 1907.

4. Hochstetter, F.: Ueber die Entwickelung der Plexus chorioidei der Seitenkammern des menschlichen Gehirns, Anat. Anz. **45**:225, 1913.

neural arches are closed [5] makes this possible, but no embryologic or experimental proof exists for this theory.

A complete review of the literature would lead to needless reduplication. We have, therefore, selected a few papers which we believe bring out the significant points concerning this subject. In considering the surgical aspect, we have chosen those reports of cases in which a considerable number of the operations were performed in one clinic, and have omitted entirely such elaborate studies as that of the Clinical Society of London,[6] for, though this study reveals many interesting facts, its value from a surgical standpoint is small, since many of the cases were observed when modern surgical methods were still in their infancy.

Fig. 1.—Section of a double spinal cord.

The occurrence of associated developmental defects of the central nervous system in cases of spina bifida has been pointed out by other observers. It is of importance in determining the prognosis in this group of cases. This point was therefore investigated. Of 29 cases that came to autopsy (no operation, 19; operation, 10), 8 showed marked defects. Six cases showed hydromyelocele. (Keiller [2] found this condition in 3 of 7 cases of spina bifida studied post mortem.) In 1 case a cleft extended along the entire dorsal aspect of the spinal cord, and in another, there was a double cord below the site of the spina bifida (fig. 1). In about 25 per cent of the cases which came to autopsy, a defect was present in addition to the spina bifida; however, 19 of these

5. Bardeen, C. R.: Manual of Human Embryology, edited by F. Keibel and F. P. Mall, Philadelphia, J. B. Lippincott Company, 1910, vol. 1.

6. Tr. Clin. Soc., London **18**:339, 1885.

cases, or about 66 per cent, were considered inoperable on account of the condition of the spina bifida. This factor, therefore, would seem to play a small rôle in establishing operative indications.

REVIEW OF LITERATURE

Surgeons may be divided into two groups in regard to their views on operation: Those who favor operation at an early age, and those who take the attitude expressed in Frazier's [7] book, that operation should be delayed until the patient is a year or more old, except when rupture of the sac is imminent. While it is true that operations performed on infants more than a year old result in a much lower mortality, it must be remembered that many of the deaths might have been prevented by early operation. The mortality of children with spina bifida who are not operated on is appalling. In the report of the Clinical Society of London,[6] in 1885, 615 of 647 deaths from spina bifida occurred in infants less than 1 year of age. Consequently, the mortality of 35 per cent reported by Moore [8] in a series of 385 cases (gathered from the literature) in children who were operated on when less than 1 year of age is not excessive. Harmer,[9] in 1917, reported a mortality of 40 per cent in a series of 34 cases in which he performed operation. In this series there were 7 patients with meningocele, 23 with myelomeningocele and 4 with cranium bifidum. Twenty-two of the patients had ulcerated or leaking sacs, and of these only 9 survived. Cutler,[10] at the Children's Hospital in Boston, analyzed 39 cases in which operation was performed. The youngest patient was 18 hours old and the oldest, 3 years. In this group there were 15 patients with simple meningocele and 24 with myelomeningocele. Thirteen of the patients had ruptured or granulating sacs. The mortality was 41 per cent. Of the patients who were discharged from the hospital, the end-result in 6 was unknown; 7 were living and well, 1 was living and improved, 4 were living but had complications and 4 had died. Of 18 patients on whom operation was not performed, 10 had died; the result in 6 was unknown, and 2 were alive.

In a recent contribution on the subject, Penfield and Cone [11] suggested a "new method" for the plastic repair of meningocele and

7. Frazier, C. H.: Survey of the Spine and Spinal Cord, New York, D. Appleton and Company, 1918, p. 265.

8. Moore, J. E.: Spina Bifida: With a Report of Three Hundred and Eighty-five Cases Treated by Excision, Surg., Gynec. & Obst. **1**:137, 1905.

9. Harmer, T. W.: Spina Bifida and Allied Malformations, Boston M. & S. J. **177**:353, 1917.

10. Cutler, G. D.: End-Results in Sixty-Two Cases of Spina Bifida and Cephalocele, Arch. Neurol. & Psychiat. **12**:149 (Aug.) 1924.

11. Penfield, W., and Cone, W.: Spina Bifida and Cranium Bifidum: Results of Plastic Repair of Meningocele and Myelomeningocele by a New Method, J. A. M. A. **98**:454 (Feb. 6) 1932.

myelomeningocele. They attempt to conserve the sac, because in the histologic study of excised meningocele sacs they have found cell nests which resemble the arachnoidal collections in the pacchionian granulations, and which they believe serve as an absorbing mechanism for the excess cerebrospinal fluid. In their series of 19 cases there was not a single death, and in no instance did hydrocephalus develop, yet in the protocols they stated that "in 4 cases noticeably large heads developed." We wonder if ventricular puncture in these 4 cases might not have shown hydrocephalus.

The preservation of the sac was suggested in 1902 by Schmidt.[12] He did not open the sac freely, but merely emptied it by puncture, involuted it and used it to fill the bony defect. In the 3 cases which he reported, the results were good.

Since there is such a divergence of opinion, it seemed desirable to collect and analyze, and to determine the results in, all cases observed in one clinic over a long period of time (twenty years) during which these cases were handled under similar conditions, and one definite policy was followed. From such a series it would seem one might draw some definite conclusions and determine the best policy to pursue.

CLINICAL MATERIAL

The present report is based on a study of 103 cases. Of these, there were 96 cases of spina bifida in infants or young children and 5 cases of cranium bifidum. The latter are included since the problem of treatment is very similar. Two cases of spina bifida occulta in young adults who presented neurologic symptoms are also included. All cases of spina bifida in which there was some function in the lower extremities and in which there was no pronounced hydrocephalus were considered suitable for operation, which was undertaken as soon as the patient's condition warranted it. If, at the time of the patient's admission, the spina bifida was ulcerated, the ulcerated area was treated until it was covered by epithelium. In some of the cases seen in the early part of the twenty year period, we operated in the presence of ulceration, but experience showed us that no matter how we prepared the area of operation, it was practically impossible to secure a clean operative field, so that today operation is delayed until the area is completely epithelialized.

ANALYSIS OF CASES

Cases in which Operation was not Performed.—Forty-six of the patients in this series were not subjected to operation. Of these, 36 died while in the hospital. Of the 10 who survived, 6 had extensive

12. Schmidt, G. B.: Ueber die Radikaloperation der Spina Bifida, Beitr. z. klin. Chir. **34**:351, 1902.

defects (rachischisis, a hopeless condition), associated with hydrocephalus and complete paralysis of the lower extremities; 4 had leaking and infected sacs and were taken from the hospital by the parents against advice while attempts were being made to secure a clean operative field. Of the 36 patients who died in the hospital, 23 were afflicted with hydrocephalus and paralysis of the lower extremities, and 1 had complete paralysis of both lower extremities without hydrocephalus. In all but 4 cases, the covering of the defect was ulcerated. Postmortem examination was done in 19 of the 36 fatal cases. The causes of death were: meningitis and hydrocephalus, 9 cases; pneumonia and hydrocephalus, 4; pyelonephritis and hydrocephalus, 3; pyelonephritis, 1; pneumonia, 1, and otitis media and hydrocephalus, 1.

It is significant that of the 19 cases that came to autopsy, hydrocephalus was present in all but 2. In addition, hydrocephalus was found clinically in 7 of the 17 cases in which an autopsy was not permitted. The causes of death in this group were: meningitis, 9 cases; pneumonia, 5; otitis media, 1, and unknown, 2.

Cases in Which Operation Was Performed.—Fifty-seven patients were subjected to operation. Twenty had simple meningocele; 27, myelomeningocele; 3, syringomyelomeningocele; 5, cranium bifidum with meningocele in 4 and myelomeningocele in 1, and 2 (adults), spina bifida occulta with disturbances of the bladder and trophic lesions of the feet. In this series, 43 of the patients with spina bifida and 4 with cranium bifidum were less than 1 year of age when operation was performed. Of the group with spina bifida, 3 were operated on during the first week of life. Ten were from 1 to 4 weeks old; 18, from 1 to 3 months old; 5, from 3 to 6 months old; 7, from 6 to 12 months old and 7, 1 year or older. Of the 20 simple meningoceles, 15 occurred in the lumbosacral region, 3 in the dorsal region and 2 in the cervical region. Of the 27 myelomeningoceles, 24 were in the lumbosacral region and 3 in the dorsal region. The 3 syringomyelomeningoceles occurred in the lumbar region.

The 50 cases of spina bifida have been divided into two groups: those in which operation was performed before 1927 and those in which operation was performed after that date. The reason for this apparent arbitrary division is that in the past five years our results have been so much better than in the previous fifteen years. This, we believe, is to be accounted for by the fact that our method of treatment in the second period had become fairly well standardized, and a much better method of closing the defects in the skin was employed. Experience and improvement in technic were undoubtedly also factors in this change, but the most important factor, we believe, was the extensive mobilization of the skin for a considerable distance on all sides of the defect before a closure was attempted.

INDICATIONS FOR OPERATION

In electing cases suitable for operation, the following points were considered:

1. In all cases of spina bifida the epithelial covering must be intact. If at the time of the patient's admission the surface was ulcerated, treatment was given until the surface became epithelialized.

2. Some movement must be present in at least one lower extremity, but it was not essential that all movements be present. There must, however, be enough movements so that when the infant grew up transplantation of muscles or stabilization of the joints could be done or braces could be worn.

3. Hydrocephalus, if present, must not be extreme. The degree of hydrocephalus was not judged by any definite measurements, but by the rate at which the head had been enlarging and by the width of the open sutures. The mere presence of hydrocephalus, however, was not considered a contraindication, for, though the treatment is vastly more complicated when one also has to deal with hydrocephalus, it is not an insurmountable problem. A question of grave importance which we are unable to answer definitely is, How large may an internal hydrocephalus be without causing mental impairment and to what extent do dilated ventricles return to normal? On the latter point, we have one important observation. Following the removal of a cerebellar tumor in a patient with dilated ventricles, ventriculographic studies were made which showed that the ventricles were greatly reduced in size and were practically normal.

4. Absence of control of the bladder, when it could be determined, was not a contraindication for operation. In a number of instances disturbances of the bladder caused us much concern when the child grew up, and some of the children have had to wear urinals. We have never transplanted ureters or performed any operation to correct this condition, though it has been discussed on a number of occasions with urologists.

5. The presence of deformities of the lower extremities, such as club feet, were not considered contraindications if the legs were sufficiently developed to permit of corrective orthopedic measures.

Of the 20 patients with simple meningocele, 2 showed evidence of hydrocephalus prior to operation, and only 2 presented evidence of weakness of the lower extremities.

Twelve of the 27 patients with myelomeningocele presented evidence of hydrocephalus before operation and 12 showed some degree of motor and sensory disturbances in the lower extremities. The correct diagnosis was not made before operation on the 3 patients with syringo-

myelomeningocele. Two of these showed evidence of hydrocephalus, and the third, paralysis of both lower extremities prior to operation.

Two adults who complained of urinary incontinence were found to have spina bifida occulta. One patient also had trophic ulcers of both feet. Laminectomy was done in both cases in an effort to alleviate the symptoms.

Congenital defects of the skull and cerebral meninges occur much less frequently than defects of the spine. In our series of 103 cases, there were 5 of cranium bifidum. All of the patients were treated surgically. The distribution in these cases was as follows: occipital meningocele in 2 infants, occipital myelomeningocele with associated hydrocephalus in 1 infant, frontal meningocele in 1 infant and meningocele at the vertex of the skull in a 6 year old girl.

Fig. 2.—Heated crib for the preoperative and the postoperative care of infants. The canvas sides can be lowered and the temperature varied by turning on more of the electric lights. The straps that hold the baby's feet can be adjusted so that the legs are kept apart and the stool drops down between the legs.

METHOD OF TREATMENT

Preoperative Care.—Infants with spina bifida tolerate operation well if certain precautions are observed. No operation is undertaken until the pediatrician has determined that the patient is tolerating his food and is in the best condition from a nutritional standpoint. Each infant is kept in a crib with a tent about it which is heated with electric light bulbs, the temperature being kept at from 95 to 98 F. (fig. 2). The child wears no clothing and no diaper and is kept lying on its abdomen on a pillow so that the legs hang down. There is no dressing over the spina bifida. The purpose of these precautions is to prevent injury to the spina bifida and all soiling of the operative field with urine or feces, which greatly increases the danger of postoperative infection. Infants tolerate these operations well if they do not lose body heat and fluid. Consequently before operation the infant receives 200 or 250 cc. of saline solution subcutaneously; then as much

Fig. 3. (M. K., table 2).—Infant with myelomeningocele.

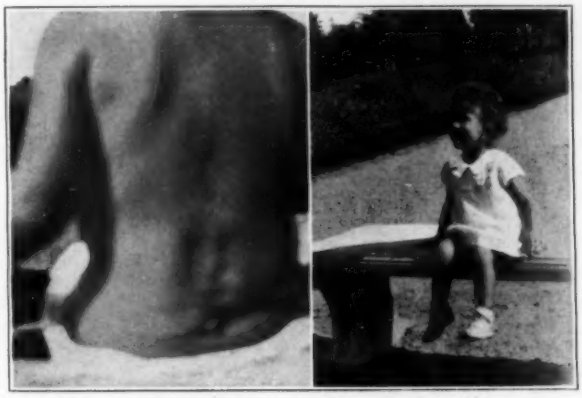

Fig. 4.—The patient in figure 3, after removal of the myelomeningocele. The small picture, taken when the child was 3 years of age, shows the droop foot, for which she wears a shoe with a right angle stop.

Fig. 5.—Cranium bifidum before and after operation.

of the infant's body is wrapped in cotton as a wide exposure of the operative field permits, and the operation is performed on a heated table. A minimal amount of ether is given, and the anesthesia is never started until the patient has been draped and the operator is standing at the table ready to begin.

Fig. 6.—Cranium bifidum before operation.

Fig. 7.—The patient shown in figure 6, after operation.

Operative Procedure.—The operation is performed in the following steps: The sac is dissected out, and the neck of the sac is exposed all around the defect in the spine. The sac is then opened, and all nerve elements are freed and replaced in the spinal canal, after meticulous hemostasis. Enough of the sac is retained to close the defect comfortably with interrupted silk sutures, without tension. We have never found any reason for attempting to save every bit of the sac, as sug-

gested recently by Penfield and Cone.[11] To fill the canal with all this excess of tissue may cause pressure on the roots. Penfield believes that saving the wall of the sac prevents the development of hydrocephalus, but in our experience this does not occur after operation as frequently as has been supposed, though one can never tell beforehand in which case it may appear. One or two flaps of the fascia of the erector spinae muscles are cut and tacked over the defect.

Then there follows what frequently is the most important and difficult part of the operation—providing ample cutaneous and subcutaneous covering for the defect. We have tried various ways of doing this, and no universal rule can be laid down for all cases, but, in the vast majority, mobilization of the skin and subcutaneous tissue for a great distance, not infrequently well forward on the lateral portion of the abdomen, is the most satisfactory procedure. Swinging pedicle flaps is not as satisfactory as the danger of a little necrosis at the edge of the flap is too great. Unfortunately, it is not feasible as a rule to make a pedicle flap according to the method of Blair, that is, cutting the flap first and moving it later.

TABLE 1.—*Follow-Up Results on Ten Patients Operated on for Myelomeningocele*

Initials	Age at Operation	Age at Time of Follow-Up	Comment
J. C.	3½ mos.	3 yrs.	Seems normal in every respect, except for slight enuresis
B. K.	4 yrs.	6 yrs.	Spastic paraplegia when operated on, no improvement
D. K.	7 days	1 yr.	Child very healthy; has club feet which are being treated
D. T.	8 mos.	5 yrs.	Walks with braces; seems normal mentally
H. A.	7 wks.	1 yr.	Slight hydrocephalus
J. M.	3 wks.	2 yrs.	Walks with braces; mentally normal
Don K.	5 wks.	3 yrs.	Healthy except for recurrent urinary infections
M. K. (figs. 3 and 4)	5 wks.	3 yrs.	Walks with braces; is still getting corrective orthopedic treatment
A. P.	19 mos.	7 yrs.	Weakness of both lower extremities; incontinence
R. F.	3 mos.	15 mos.	Seems normal

Postoperative Care.—After the operation, the child is kept on its abdomen in the enclosed heated crib until the wound is healed. Careful measurements of the size of the head and the tenseness of the fontanels are made. Fluids are restricted if there is a tendency for the head to enlarge.

FOLLOW-UP RESULTS

Since end-results are of vital importance in a study of this type, an effort was made to get in touch with all the patients on whom operation was performed. Of the 38 patients who were discharged from the hospital, answers were received concerning 26.

Of the 26, 11 had had simple meningocele; 10 of these were well in every respect and 1 child (D. H.) who had had a high dorsal meningocele was in good health but was said to show slight awkwardness in using his fingers.

Of the remaining 15 patients, 12 had had myelomeningocele; 2 of these died from an undetermined cause shortly after discharge from the hospital. The results in the remaining 10 are shown in table 1. Of

the 4 patients with cranium bifidum and associated meningocele, follow-up records were available on 3. All were living and in good health (figs. 5, 6 and 7).

TABLE 2.—*Data on Patients Operated on Between 1912 and 1927*

Initials and Sex*	Date and Age	Type	Hydrocephalus	Paralysis	Resulting Hydrocephalus	Immediate Results	Comment
M. O. ♀	7/19/12 8 yrs.	Lumbar meningocele	No	Club feet; awkward gait	No	Not improved	Incontinence
C. D. ♀	9/19/14 3 mos.	Myelomeningocele	Slight	No	Yes	Poor	Infection of wound
R. B. ♀	1/ 6/16 10 days	Syringomyelocele; coverings ulcerated	Yes	No	Yes	Died	Meningitis 2 wks. after operation
R. D. ♂	2/16/16 6 wks.	Myelomeningocele; coverings ulcerated	Yes	Complete, both lower extremities	....	Died	Meningitis 3 wks. after operation
P. H. ♂	9/ 7/18 5 wks.	Dorsal (fourth and fifth) myelomeningocele	No	No	No	Good	
C. S. ♀	2/ 5/19 10 mos.	Myelomeningocele	No	No	No	Died	Pyelonephritis 3 wks. after operation
R. F. ♀	9/18/19 3 mos.	Myelomeningocele	No	Both lower extremities	No	Good	Seen 1 yr. later; uses legs satisfactorily
A. P. ♀	11/3/19 1 yr., 7 mos.	Myelomeningocele	Slight	No	No increase in hydrocephalus	Weakness of both legs after operation	Seen 5 yrs. later, cauda equina syndrome
A. H. ♀	12/19/19 6 days	Meningocele; coverings ulcerated	No	No	No	Infection of wound	Infection on admission
L. J. ♀	3/24/20 7 mos.	Meningocele	No	No	....	Died	Pneumonia third day after operation
L. R. ♂	6/21/20 11 mos.	Meningocele with dermoid cyst	No	No	No	Good	
W. J. ♂	9/28/21 8 mos.	Dorsal meningocele	Yes	No	Increased	Choroidoplexectomy 2 wks. later	Death third day after operation
B. S. ♀	12/6/22 3 wks.	Meningocele	Slight	No	Increased	Died	Pneumonia; increasing hydrocephalus
B. D. ♂	9/ 5/23 16 days	Myelomeningocele	No	No	Yes	Choroidoplexectomy at 5½ wks.	Died same day
B. J. ♀	10/5/23 7 days	Dorsal meningocele	No	No	No	Good	
K. D. ♂	12/11/24 6 wks.	Myelomeningocele; sac infected	No	No	Yes	Died	Pneumonia and basilar meningitis at 7 wks.
B. E. ♂	11/9/25 2 wks.	Lumbar meningocele	No	No	No	Good	Seen at 2 yrs.; child normal
C. E. ♀	1/ 9/25 19 mos.	Syringomyelocele	Yes	Lower extremities	....	Died	Death 2 hrs. after operation
L. W. ♀	5/12/25 1 mo.	Myelomeningocele	No	No	No	Improved	Mild meningitis developed; recovery
A. F. ♀	7/11/26 7 mos.	Low dorsal and lumbar syringomyelocele	No	No	....	Died	Death on first day after operation

* In this column, ♂ indicates male; ♀, female.

COMMENT

The mortality following operation in cases of spina bifida and cranium bifidum, according to the literature, has ranged between 40 and 50 per cent when the operations were performed early in life.

TABLE 3.—*Data on Patients Operated on Between 1927 and 1932*

Initials and Sex*	Date and Age	Type	Hydrocephalus	Paralysis	Resulting Hydrocephalus	Immediate Results	Comment
D. T. ♀	3/28/27 8 mos.	Lumbar meningomyelocele	Yes	Both lower extremities	No increase	Good	Follow-up in 5 yrs.; walks with brace; incontinence
B. G. ♀	5/19/27 2 mos.	Myelomeningocele; infected sac	Yes	Both lower extremities spastic	....	Died; meningitis	
B. B. ♀	6/ 5/27 3 mos.	Low dorsal myelomeningocele	Yes	No	Increase in hydrocephalus	Poor	Died after a few weeks at home
D. K. ♂	3/21/27 5 wks.	Myelomeningocele	No	No	No	Good	Seen 3 yrs. later; urinary infection
D. H. ♂	10/15/27 3 yrs.	High dorsal meningocele	No	Both lower extremities; bilateral ankle clonus	No	Excellent	Follow-up in 5 yrs.; cured; walks
W. W. ♂	12/30/27 3 wks.	Myelomeningocele	Yes	Both lower extremities	Yes	Poor	Seen at 18 mos.; club feet; trophic ulcers
J. H. ♀	10/25/27 5½ mos.	Myelomeningocele	No	No	No	Good	Died 11/13/27; cause unknown
M. Z. ♀	5/31/28 8 mos.	Cervical meningocele	No	No	No	Good	
R. H. ♀	8/14/29 2½ mos.	Myelomeningocele	Yes	Partial	....	Died	Hyperthermia 30 hrs. after operation
C. F. ♀	7/11/29 2 yrs., 4 mos.	Myelomeningocele	No	Both lower extremities	No	Good	Power in legs increasing
J. B. ♂	10/8/29 1 mo.	Meningocele	No	No	No	Good	Letter 2/10/33 stating "He is very healthy"
J. R. ♀	9/ 8/29 5 wks.	Meningocele	No	No	No	Good	Sac invaginated into canal; normal 3 yrs. later
L. H. ♀	11/1/29 2 mos.	Cervical meningocele	No	No	No	Good	Follow-up 2/14/33; normal in every way
A. W. ♀	11/9/29 2 mos.	Meningocele	No	No	No	Died	
J. M. ♂	11/21/29 3 wks.	Myelomeningocele	No	Weakness of lower extremities	No	Improved	Follow-up 2/24/31; extremities stronger; walks with braces
J. C. ♀	9/21/30 3½ mos.	Myelomeningocele	Yes	No	Slight increase	Same	Follow-up 2/14/33; "seems normal in every way"
M. M. ♀	9/21/28 2 mos.	Myelomeningocele	Slight	Lower extremity	....	Died	Death 2 wks. after operation
B. C. ♂	3/10/30 6 wks.	Myelomeningocele	Yes	Both lower extremities	Increase in hydrocephalus	Died	Pneumonia 4 wks. after operation
M. K. ♀ (fig. 3 and 4)	4/28/30 5 wks.	Myelomeningocele	No	Right foot	No	Good	Follow-up Nov., 1932; excellent health; walks with braces
B. C. ♂	5/ 7/30 10 days	Myelomeningocele	No	No	No	Good	
L. W. ♀	11/20/30 2 mos.	Meningocele	No	No	No	Good	
J. D. ♀	11/30/30 1 yr.	Meningocele	No	No	No	Good	Child normal at 3 yrs.
E. J. ♂	1/28/31 3 mos.	Meningocele	No	No	No	Good	Follow-up 2/21/33; "perfect in every way"
F. R. ♂	2/ 9/31 4 mos.	Meningocele	No	No	No	Good	Follow-up 2/24/33; "normal in every way"

* In this column, ♂ indicates male; ♀, female.

TABLE 3.—*Data on Patients Operated on Between 1927 and 1932—Continued*

Initials and Sex	Date and Age	Type	Hydrocephalus	Paralysis	Resulting Hydrocephalus	Immediate Results	Comment
B. K. ♀	5/15/31 4 yrs.	Myelomeningocele	No	Sensory loss below second dorsal vertebrae; spastic paraplegia	No	Same	Follow-up 2/16/33; no change in condition; still has spastic paraplegia
H. A. ♀	11/27/31 7 wks.	Myelomeningocele	No	No	Slight	Poor ?	Follow-up Oct., 1932; has slight hydrocephalus
D. K. ♀	1/ 6/32 7 days	Myelomeningocele	No	No	No	Good	Child is well except for club feet
W. B. ♂	4/29/23 2 mos.	Meningocele with sacral teratoma	No	No	No	Good	Follow-up 2/16/33; "baby getting along just fine"
N. E. ♀	5/11/32 2 wks.	Meningocele	No	No	No	Good	Follow-up 2/11/33; "in very good health"
P. M. ♂	5/ 2/32 3 mos.	Dorsal myelomeningocele	Slight	No	....	Died	Hyperthermia

Recently Penfield and Cone [11] reported 21 cases in which operation was performed with only 2 deaths, and Coughlin,[13] 12 cases with 1 death. In our own series, operation was performed in 50 cases of spina bifida with 14 deaths and in 5 cases of cranium bifidum with 1 death, a mortality of 27 per cent. Forty-seven of our patients were less than 1 year old. Because of the marked improvement in results since 1927, we divided our cases of spina bifida into two groups. Table 2 includes data on those cases in which operation was performed from 1912 to 1927. In this group there were 20 cases of spina bifida with 8 deaths (40 per cent mortality); in addition, in 2 of the cases a marked degree of hydrocephalus developed for which choroidoplexectomy was done with subsequent fatality. In table 3 are presented data on the cases in which operation was performed during the second period (from 1927 to 1932). There were 30 cases of spina bifida in this group with 6 deaths, a mortality of 20 per cent. As stated before, the marked improvement in the results since 1927 was due to several factors; however, it is significant that of the 8 patients who died prior to 1927, 3 had infected sacs at the time of operation and died subsequently of meningitis. Since 1927, only 1 patient (B. G., table 3) with an infected sac has been operated on, and the fatality was also due to meningitis. The data in the cases of cranium bifidum are listed in table 4.

The frequency with which hydrocephalus developed after the repair of a spina bifida is indicated in the tables. In patients with simple

13. Coughlin, W. T.: Spina Bifida: A Clinical Study with a Report of Twelve Personal Cases, Ann. Surg. **94**:892, 1931.

meningocele, this was relatively uncommon. Of 20 patients, 2 had a mild degree of hydrocephalus before operation which increased following the repair of the spina bifida. Weakness of the lower extremities occurred only twice in patients with simple meningocele. In a child of 3 years (D. H., table 3), with a high dorsal meningocele, there was a bilateral ankle clonus and inability to walk. Five years after operation the child walked normally and was pronounced "cured" by the family physician. In cases in which nerve tissue was present in the sac, the incidence of hydrocephalus and paralysis of the lower extremities before and after operation was much greater than in cases with simple meningocele. Of 27 patients with myelomeningocele, 10 were afflicted with some degree of hydrocephalus prior to operation. Following repair of the spina bifida, the hydrocephalus increased in 5; in 2 there was no

TABLE 4.—*Data on Patients with Cranium Bifidum*

Initials and Sex*	Date and Age	Type	Hydrocephalus	Resulting Hydrocephalus	Immediate Result	Comment
A. H. ♀	5/ 9/21 3 mos.	Occipital meningocele	No	No	Good	Infant seen at 9 mos. of age; seemed normal
S. D. ♀	2/ 3/26 6 yrs.	Meningocele at vertex	No	No	Good	
G. R. ♀	4/20/27 3 days	Occipital myelomeningocele	Slight hydrocephalus	...	Died 5 wks. after operation	Necropsy showed absence of median lobe of cerebellum
H. K. ♀	1/27/27 12 days	Frontal meningocele	No	No	Good	Follow-up 2/27/33; "baby perfect"
L. G. H. ♂	10/20/30 6 mos.	Occipital meningocele	No	No	Good	Follow-up 2/16/33; "he is just fine"

* In this column, ♂ indicates male; ♀, female.

change, and the remaining 3 died shortly after operation. In 2 infants in whom enlargement of the head was not noted prior to operation hydrocephalus developed after repair of the spina bifida. It is interesting to note that in the group of 46 patients who were not operated on, 29 had hydrocephalus. Weakness of the lower extremities was present prior to operation in 10 patients with myelomeningocele. An improvement in the strength of the lower extremities followed operation in 5 cases; there was no improvement in 2, and death occurred shortly after operation in 3.

Of the 2 adults who were subjected to laminectomy because of neurologic symptoms associated with spina bifida occulta, 1 showed marked improvement in the control of the bladder and the trophic ulcers promptly healed. The second patient showed no improvement.

Five patients with cranium bifidum (table 4) were included in this study because of the marked similarity of this defect to spina bifida. The operative procedure in each case was similar to that employed in the repair of spina bifida. Four patients made satisfactory recoveries

without sequelae or complications. One infant, 3 days old, died five weeks after operation. Autopsy revealed complete absence of the median lobe of the cerebellum and a slight internal hydrocephalus. In addition, bronchopneumonia and acute purulent ependymitis were present.

SUMMARY

1. Fifty cases of spina bifida and 5 cases of cranium bifidum in which surgical treatment was carried out in one clinic have been analyzed.

2. Of 22 patients who were operated on before 1927, 10 died; of 33 operated on since 1927, only 6 died.

3. Patients with simple meningocele rarely have hydrocephalus or paralysis of the lower extremities prior to operation, and the follow-up histories obtained in 14 cases (11 cases of spina bifida with meningocele and 3 cases of cranium bifidum with meningocele) indicate that these children grow up normally following operation and rarely have any permanent serious disability.

4. When nerve tissue is present in the sac (cases with myelomeningocele or syringomyelomeningocele), however, hydrocephalus and weakness of the lower extremities are a frequent complication prior to operation. Though these symptoms persist, it is rather striking that the general idea that hydrocephalus will develop, even if it is not present before operation, does not seem to be supported by our experience. The conclusion that the type of closure is responsible for postoperative hydrocephalus does not seem justified.

In our series, almost 50 per cent of the patients developed normally (12 of 22).

HISTOLOGIC STUDIES OF AUTOGENOUS AND HOMOGENOUS TRANSPLANTS OF THE KIDNEY

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An autogenous transplant of the kidney will function normally or maintain the life of the animal for several months or years. On the other hand, a homogenous transplant of the kidney will excrete urine for only a limited period and then rather abruptly cease to function. This peculiarity in the behavior of the homogenous transplant has been variously explained, but without the support of any definite evidence explanations can at best be purely hypothetic. Although it seems obvious that some light might be shed on the subject by knowledge of the histologic changes which take place in a homogenous transplanted kidney both before and after it has failed to excrete urine, such data are yet to be obtained.

The purpose of this investigation is to study the histologic changes that take place in the transplanted kidneys from day to day and to note any qualitative or quantitative difference in the kaleidoscopic picture between the autogenous and the homogenous types of transplants, as well as between the functioning and the nonfunctioning homotransplants.

SUMMARY OF THE LITERATURE

Autogenous transplants of the kidney have been found normal in size, color, consistence and microscopic appearance three weeks,[1] twenty-five days,[2] seventy-nine days and almost a year after operation.[3] On

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1. Capelle: Ueber Dauerresultate nach Gefäss- und Organtransplantationen, Berl. klin. Wchnschr. **45**:2012 (Nov. 9) 1908. Stich, Rudolf: Zur Transplantation von Organen mittelst Gefässnaht, Arch. f. klin. Chir. **83**:494, 1907.

2. Lobenhoffer, Wilhelm: Funktionsprüfungen an transplantierten Nieren, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **26**:197, 1913

3. Carrel, Alexis: Doppelte Nephrektomie und Reimplantation einer Niere, Arch. f. klin. Chir. **88**:379, 1909.

the other hand, Carrel,[4] Lobenhoffer,[2] Lurz,[5] Williamson[6] and Holloway[7] observed certain definite anatomic changes which accompanied the physiologic and pathologic processes prevailing in the transplanted organ. During the first few days, the microscopic pictures were such as would be expected after manipulating the organ, severing all the nerves and temporarily interrupting the circulation. No alteration in the histologic appearance took place until the function began to fail. Finally, the usual picture of hydronephrosis and infection prevailed.

In the case of the homogenous transplants, the kidneys have been found to be more or less normal two, twelve, fifty, seventy-one[8] and thirty-five days after homotransplantation.[9] However, these experiences are extraordinary. Usually, the homotransplants are subject to a great variety of lesions. Areas of infarction have been observed after the first or second day.[10] Partial or complete necrosis or gangrene of the kidney has taken place after forty hours,[11] one to eight days,[12] from five to eight days,[10] ten days or less[13] and from fourteen to eighteen days.[14] Calcification of the necrosed tubules has been noted after eighteen days. Absorption of the renal substance may begin on the fifteenth[10] day and be completed in three months.[13] The organ has been seen to become fibrosed in seventy-four days.[13] Hydronephrosis has been known to develop in six and fourteen days.[9]

Soon after transplantation, the homogenous kidney presents the microscopic picture of nephrosis. The glomeruli are normal. Desqua-

4. Carrel, Alexis: Remote Results of the Replantation of the Kidney and the Spleen, J. Exper. Med. **12**:146, 1910; footnote 3.

5. Lurz, L.: Ueber Nierentransplantationen: Vergleichende Untersuchungen des Urins und der Uretertätigkeit der autotransplantierten und der normalen Niere, Deutsche Ztschr. f. Chir. **194**:25, 1925.

6. Williamson, C. S.: Further Studies on the Transplantation of the Kidney, J. Urol. **16**:231, 1926.

7. Holloway, J. K.: The Effect of Diuretics on the Transplanted Kidneys, J. Urol. **15**:111, 1926.

8. Avramovici, Aurel: Les transplantations du rein (étude expérimentale), Lyon chir. **21**:734 (Nov.-Dec.) 1924.

9. Carrel, Alexis: Transplantation in Mass of the Kidneys, J. Exper. Med. **10**:98, 1908.

10. Mantelli, Candido: Esperienze sul trapianto dei reni, Pathologica **5**:69 (Feb. 1) 1913.

11. Decastello, A. V.: Ueber experimentelle Nierentransplantation, Wien. klin. Wchnschr. **15**:317 (March 20) 1902.

12. Floresco, N.: Recherches sur la transplantation du rein, J. de physiol. et de path. gén. **7**:47, 1905.

13. Villard, E., and Perrin, E.: Transplantations rénales, Lyon chir. **10**:109 (Aug. 1) 1913.

14. Borst and Enderlen: Ueber Transplantation von Gefässen und ganzen Organen, Deutsche Ztschr. f. Chir. **99**:54, 1909.

mation of the epithelial cells takes place. Coarse granulation and fatty degeneration affect the tubular epithelium, particularly that of the proximal convoluted tubules and the thick limbs of Henle's loops. Many of the thin limbs of Henle's loops and the collecting tubules contain casts.[15]

When the transplant was functioning more or less well, Williamson found a moderate amount of edema of the tubules. Occasionally some hyalin-like material was present in the collecting tubules. Ibuka noted cloudy swelling or degeneration of the renal parenchyma of varying degree. Shortly afterward, Williamson noticed early changes in the glomeruli and some lymphocytic infiltration with little alteration in the tubular elements. Then the glomeruli became more intensely congested, sometimes with the diapedesis of an erythrocyte into the capsular spaces. The swelling of the epithelial cells lining the tubules increased; the nuclei stained poorly, and occasionally actual degeneration was evident. A few polymorphonuclear leukocytes also appeared at this stage. Ibuka[15] observed progressive injury to the glomeruli and the tubules, represented in the extreme by fatty degeneration of the capillary tufts of the glomeruli and necrosis of the tubular epithelium.

As the functional life of the transplant comes to an end either a predominating glomerular type of injury or overwhelming tubular lesions prevail, depending on whether the process of failure is rapid or relatively slow. When ascending infection supervenes, abscesses, rarely cortical in distribution, may be formed and replacement of the renal parenchyma by fibrous tissue may take place.[6]

MATERIALS AND METHODS OF STUDY

For this study, twenty-four transplantations of the kidney were performed. Six of these composed a series of autogenous transplantations of the kidney, and they served as controls for another series of eighteen homogenous transplantations of the kidney.

Sixty biopsies were made. The specimens were fixed in Zenker's solution as soon as they were obtained. Three kinds of stains were used, hematoxylin and eosin, Mallory's phosphotungstic acid and hematoxylin and van Gieson's alum-hematoxylin, trinitrophenol and acid fuchsin. A total of one hundred and eighty sections was studied.

Medium-sized, short-haired, quiet dogs were selected. In the case of homotransplantation, the host and the donor were selected at random without any particular reference to their breed, sex or age. The animals were maintained on the regular kennel diet consisting of biscuits, milk, syrup and water, and an occasional allowance of meat. Unless the excretion from the transplanted kidney was

15. Ibuka, Kenji: Function of the Homogenous Kidney Transplant, Am. J. M. Sc. **171**:420, 1926.

unusually profuse, 10 cc. of a 10 per cent solution of dextrose in physiologic solution of sodium chloride per kilogram of body weight was generally administered by the intravenous route just prior to the time for the collection of a preoperative specimen of urine.

The function of the transplanted kidney was estimated quantitatively by the results of chemical analyses of its excretion. As the general condition of the animal, the kind and amount of food and fluid intake, the details of the operation and environmental factors varied from day to day, the absolute values were of little significance without a certain standard of comparison. The function of the normal kidney in the case of autotransplantation and that of the host's kidneys in the case of homotransplantation served as such a criterion.

Every day immediately preceding the biopsy operation, a specimen of urine was collected from the transplant, and another one was obtained simultaneously by catheterization from the bladder. The concentrations of urea and ammonia nitrogen and creatinine in the urine were determined by the colorimetric methods of Folin and that of sodium chloride by the titration method of Whitehorn.

The operative procedures included transplantation and biopsy every twenty-four hours thereafter. All the operations were performed under ether anesthesia and with the strictest aseptic precautions. The operative field was shaved and washed with soap and water. It was then cleansed with a fat solvent and painted with two coats of a 2 per cent solution of iodine in benzene. Twenty-day 00 chromic catgut was used for suturing the muscles and the subcutaneous fascia, and linen for suturing the peritoneum and the skin. At the conclusion of the operation both the abdominal and the cervical wound were painted with iodine, and a dressing of collodion gauze was applied on the former and not on the latter.

Transplantation.—The sequence of the main events in transplantation consisted of: (1) the choice of a kidney as the transplant, (2) the preparation of the vessels in the neck for suturing, (3) nephrectomy and (4) vascular anastomoses. Except for the fact that two animals, a host and a donor, were used in homotransplantation, the technic was entirely the same for both varieties of transplantation.

Choice of a Kidney: A median line incision of the abdomen was made. The left kidney was mobilized by detachment from the surrounding fascia and ligaments, care being taken to leave the renal capsule intact. The renal vessels were isolated and examined. When it was found that the renal artery bifurcated close to its origin or that two separate renal arteries arose from the aorta, the right kidney had to be used.

Preparation of the Vessels in the Neck: A median line incision was made in the neck. Either side of the neck may be used. The common carotid artery was exposed, and a pocket to receive the transplant was made by separating the muscle by blunt dissection. The vessel was isolated and its adventitia removed for a distance of from 5 to 6 cm. A bull-dog clamp with padded blades was applied to the proximal end of the segment and a hemostat clamp to the distal end. The segment was divided with a sharp knife about 1 cm. above the proximal clamp. The distal end was ligated with linen and the portion proximal to the clamp excised. Any adventitia remaining attached to the proximal end of the vessel was then removed. Liquid petrolatum was applied to both sides of the vessel wall. A sponge saturated in warm saline solution was placed over it until the time to make the anastomosis.

The external jugular vein was prepared in a similar manner. The proximal end was then carried mesially through the fascia beneath the sternocleidomastoid muscle and placed under a sponge moistened with warm saline solution.

Nephrectomy: Two large curved clamps were applied on both the renal artery and the renal vein close to their origin from the aorta and the vena cava, respectively. The artery was clamped before the vein. The vessels were severed distal to the clamps. The ureter was freed and cut, with two thirds of it attached to the kidney. The kidney was not perfused. It was wrapped in a pack dipped in warm saline solution and was gently pressed between the hands.

When the transplantation of the kidney was completed, the renal vessels were doubly ligated with linen, and the abdominal wound was closed.

Vascular Anastomosis: After removal of the adventitia from the renal vessels the ends were cut even. The kidney was rotated 180 degrees on its long axis and placed on its convex border. The carotid artery was anastomosed to the renal artery before the external jugular vein was anastomosed to the renal vein.

Three sutures of 000 silk on straight number 16 needles were passed through both the media and the intima of the prepared ends of the vessels at points equidistant from one another. The ends of the vessels were brought together, and after the sutures were tied and held under a moderate amount of tension the vessels assumed a triangular shape. By rotation, first one side and then the other was held in the horizontal plane and sewed with a continuous through-and-through suture. One needle and suture was used for each side or for all three sides and tied to the next so-called stay suture.

After the anastomosis had been completed, first the clamp on the external jugular vein and then that on the common carotid artery were removed. Any bleeding from the suture line usually ceased after the application of digital pressure or heat, and occasionally after repair with one or two additional sutures.

The time when the first clamp was applied to the renal artery and the time when the clamp was removed from the common carotid artery were always noted. During that interval there was no circulation of blood through the kidney.

A catheter of suitable size was inserted into the ureter until the upper end reached the pelviureteral juncture. The distal end of the ureter was tied to hold the catheter in place as well as to stop bleeding from the ureteral vessels. The ureter was then passed under the sternocleidomastoid muscle and brought out through a stab wound in the skin on the other side of the neck. About 2 cm. of the ureteral stump was allowed to protrude beyond the surface of the skin and was held snugly in a tunnel formed by suturing the skin over it.

Biopsy.—For biopsies, the general surgical procedures remained essentially the same. The wound of the primary operation in the neck was opened. The transplanted kidney was freed from the surrounding tissues and lifted out of the muscle pocket. The artery was compressed by digital pressure, while a wedge-shaped piece of tissue, 2 by 1 by 0.5 cm., was excised from the convex border of the kidney. The specimen for the first biopsy was removed from midway between the two poles, and subsequently it was obtained from one side and then from the other alternately. The sites were so spaced as to include between them at least 1 cm. of renal substance.

The biopsy wound was closed with number 2 twenty-day chromic catgut by the use of two deeply placed interrupted mattress sutures and a superficial layer of continuous suture. The mattress sutures were knotted on opposite sides. For the first suture, the end carrying a number 8 long straight needle was cut short, whereas for the second, the reverse was done. For the continuous layer, the

suture was passed diagonally across the wound, first laterally to one extremity of the line of excision, then mesially to the center and finally laterally again to the other extremity, returning each time straight through the renal substance to the same side. At the conclusion it was tied to the end of the first mattress suture which was left long on the other side.

RESULTS OF INVESTIGATION

General Observations.—Of a total of twenty-four transplantations of the kidney, six were failures from the point of view of this study. Thrombosis in the renal vessels with infarction and necrosis of the kidney within twenty-four hours after transplantation occurred once in the autotransplantation series and twice in the homotransplantation series. One dog died before the operation of homotransplantation was completed, and another dog died of hemorrhage in less than a day after the transplantation of a homogenous kidney. In the sixth dog the transplanted kidney showed marked arteriosclerotic changes.

On the average it took an hour and fifty-six minutes to perform an autotransplantation and an hour and twenty-seven minutes to do a homotransplantation. The time which elapsed before the circulation through the transplanted kidney could be restored was thirty-two and a half minutes in the autotransplantation series, and twenty-seven and a half minutes in the homotransplantation series.

Three of the autogenous transplants of the kidney and six of the homotransplants functioned well during the entire period of observation, ranging from two to five days for the former and from one to five days for the latter. Two autotransplants functioned for two of three days, and one homotransplant functioned satisfactorily for only one of five days. Seven other homogenous transplants failed to excrete urine at any time. In these cases exploration revealed no thrombosis in the renal vessels. The biopsy wounds bled freely and healed well.

The average duration of the functional activity was seventy-two hours for the whole series of autogenous transplants and thirty-one hours for homogenous transplants. Leaving the nonfunctioning group out of consideration, we found that the homogenous transplants functioned for an average of fifty-eight hours.

So far as the results of urinalysis were concerned, there was no significant difference between the two varieties of transplants. The urine was generally pale. It was neutral or alkaline in reaction. Albuminuria was constant, although the quantity varied from a trace to a large amount. The sediment obtained after centrifugation contained a varying number of hyaline and granular casts, pus cells and erythrocytes. The concentration of urea and ammonia nitrogen and creatinine occasionally attained a high level but never equaled or exceeded that found in the urine of the normal kidney or kidneys. With few excep-

tions, the transplant secreted a far greater amount of sodium chloride per cubic centimeter of urine than the normal kidney or kidneys.

In the group of five autogenous transplants the experiment was terminated by death in four animals and by thrombosis in the renal vessels in one. In the group of thirteen experiments on homotransplantation the experiment was terminated by death in one animal and by thrombosis in the renal artery or vein, or both, in seven. In the remaining five experiments the transplanted kidney was purposely removed at operation.

The amount of serosanguineous exudate around the transplant in the muscle pocket and the intensity of the inflammatory reaction of the surrounding tissues and the overlying skin varied considerably. The general impression, however, was that they were much greater in the case of the homogenous than in the case of the autogenous transplants.

Histologic Observations.—The results of the experiments will be considered in three groups: (1) autogenous transplants; (2) functioning homogenous transplants, and (3) nonfunctioning homogenous transplants. The essential histologic observations and the complete protocols of the most representative experiment in each group are as follows:

Autogenous Transplants: The glomeruli were normal. Sometimes there was an albuminoid material in a few capsular spaces. The tubules at times appeared normal for the first one or two days and then revealed swelling and granular degeneration or hyalinization to a varying extent; or at times they showed the degenerative changes in the beginning and, after one or two days, either proceeded to hyalinize or resumed a more normal appearance. A varying number of tubules generally contained an albuminoid material in their lumens. In association with extensive polymorphonuclear leukocytic infiltration or necrosis, the content at times was cellular. A small number of tubules showed more or less dilatation of their lumens on the fourth and fifth days. The interstitial tissue generally showed only a few small areas of congestion or an occasional collection of mononuclear cells throughout the period of observation. Occasionally, however, it showed a progressively increasing amount of congestion and mononuclear cellular infiltration. In two experiments there was polymorphonuclear leukocytic infiltration with or without necrosis on the second day. In one of those cases, a large portion of the renal parenchyma was found to have been destroyed on the third day. The capsule of the kidney usually showed a varying amount of extravasation, formation of fibrin and polymorphonuclear leukocytic infiltration on the first one or two days. Organization then set in and an increasing amount of fibrous tissue was formed.

The following is the illustrative protocol for experiment 1 (fig. 1).

The experiment was started on April 7, 1931. The animal was an adult female shepherd dog, weighing 16.9 Kg. An autogenous kidney was transplanted. The time of the operation was from 9 to 11 a. m. The circulation to the transplanted kidney was restored in forty minutes.

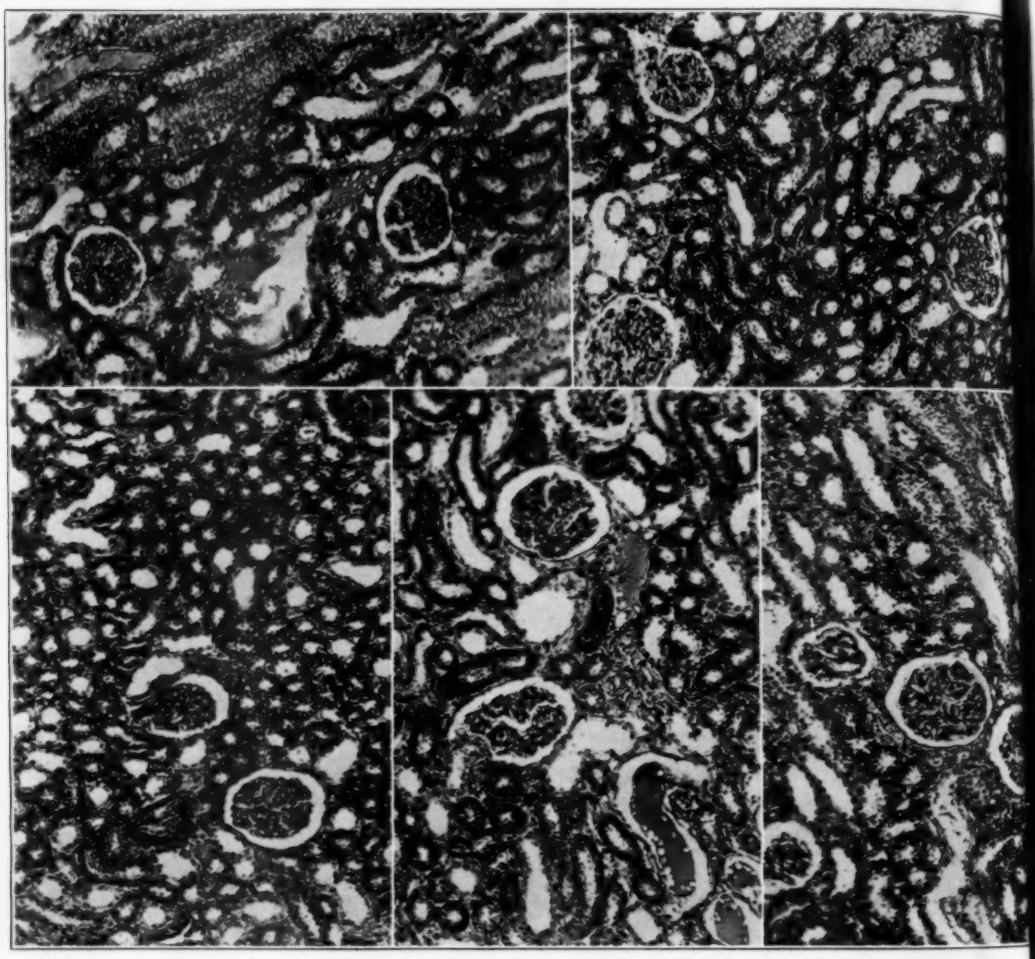

Fig. 1.—Histologic appearance of an autogenous transplant of the kidney from day to day (× 130).

At the end of twenty-four hours the urinary excretion was profuse. Each cubic centimeter contained 1.080 mg. of urea and ammonia nitrogen (3.920 mg. from the normal kidney) and 0.384 mg. of creatinine (0.485 mg. from the normal kidney). The glomeruli were normal. There was a small amount of albuminoid material in a few capsular spaces. The epithelial cells lining many clusters of tubules were swollen, and their cytoplasm was granular, but their nuclei appeared

normal. Some of the tubules contained albuminoid material in their lumens. The interstitial tissue was normal. The capsule of the kidney revealed some extravasation and polymorphonuclear leukocytic infiltration.

At the end of forty-eight hours the urinary excretion was profuse. Each cubic centimeter contained 1.568 mg. of urea and ammonia nitrogen (1.950 mg. from the normal kidney), 0.259 mg. of creatinine (0.341 mg. from the normal kidney) and 1.650 mg. of sodium chloride (1.800 mg. from the normal kidney). The excretion of phenolsulphonphthalein during the first hour after the intravenous injection of 1 cc. of the dye was 7.4 per cent for the transplant as compared with 9.1 per cent for the normal kidney. The glomeruli were normal. Many of the tubules showed swelling and granular degeneration of the epithelial cells. Albuminoid material was present in the lumens of a few tubules. There was some congestion here and there in the interstitial tissue. The capsule of the kidney revealed extravasation, formation of fibrin, many polymorphonuclear leukocytes and a few fibroblasts.

At seventy-two hours the urinary excretion was good. Each cubic centimeter contained 1.850 mg. of urea and ammonia nitrogen (3.900 mg. from the normal kidney), 0.546 mg. of creatinine (0.526 mg. from the normal kidney) and 3.900 mg. of sodium chloride (2.370 mg. from the normal kidney). The glomeruli as well as the tubules were normal. The lumens of a few tubules contained albuminoid material. A few small areas of congestion were noted in the interstitial tissue. The capsule of the kidney showed extravasation, polymorphonuclear leukocytic infiltration, active proliferation of the fibroblasts and an increased amount of fibrous tissue.

At ninety-six hours the urinary excretion was scanty. Each cubic centimeter contained 0.714 mg. of urea and ammonia nitrogen (4.115 mg. from the normal kidney). The glomeruli were normal. The lumens of the tubules were dilated. The lumens of a few of the tubules contained albuminoid material. The interstitial tissue was normal. The capsule of the kidney showed extravasation, polymorphonuclear leukocytic infiltration, formation of new capillaries, active proliferation of the fibroblasts and an increased amount of fibrous tissue.

At the end of one hundred and twenty hours the urinary excretion was scanty. Each cubic centimeter contained 0.314 mg. of urea and ammonia nitrogen (2.272 mg. from the normal kidney). The glomeruli appeared somewhat smaller than usual. Marked granular degeneration of the epithelial cells was present in many of the tubules; in some there was cystic dilatation of the lumens, whereas a few other tubules contained albuminoid material. There were several small areas of congestion scattered throughout the interstitial tissue. The capsule of the kidney showed extravasation, formation of fibrin, polymorphonuclear leukocytic infiltration, active proliferation of the fibroblasts and an increased amount of fibrous tissue.

At the end of one hundred and forty-four hours the dog died of hemorrhage from a tear in the vein at the site of anastomosis. The transplanted kidney weighed 75 Gm., measured 7 by 4.5 by 4 cm. and showed a cloudy swelling. The normal kidney weighed 75 Gm. and measured 6.5 by 4 by 2.5 cm.

Functioning Homogenous Transplants: The glomeruli were normal. Albuminoid material was found in a few capsular spaces on the first two days in one of the experiments. The tubules usually appeared essentially normal for the first one or two days and then exhibited an increasing amount of swelling and granular degeneration or hyaliniza-

tion. On the other hand, the degenerative changes were observed on the first day, either to remain or to disappear later. Occasionally there was dilatation in the lumens of the tubules, which was evident either from the beginning or only toward the end of the experiment. With but one exception a varying number of tubules always contained albuminoid material. The interstitial tissue was normal on the first day. More commonly, however, a few collections of mononuclear cells and areas of congestion were present in the beginning, and they gradually increased in extent and intensity from day to day. Polymorphonuclear leukocytic infiltration, which occurred in several instances, was always found on the last day of the experiment. In one case the polymorphonuclear leukocytes were absent, and the necrosis seemed to be the consummation of a progressively increasing infiltration of mononuclear cells. The capsule of the kidney was the seat of extravasation, formation of fibrin and polymorphonuclear leukocytic infiltration until the second or third day, when organization and fibrosis began.

The illustrative protocol of experiment 11 (fig. 2) is as follows:

On October 12, 1931, a homogenous kidney was transplanted into an adult male shepherd dog weighing 14.8 Kg. The donor was an adult male shepherd dog weighing 10.3 Kg. The time was from 8:45 to 10:20 a. m. The circulation to the transplanted kidney was restored in twenty-five minutes. Immediately there was albuminoid material in a few capsular spaces and tubules. Otherwise the capsule of the kidney and the parenchyma were normal.

At the end of twenty-four hours the urinary excretion was profuse. Each cubic centimeter contained 2.284 mg. of urea and ammonia nitrogen (22.220 mg. from the recipient's kidneys), 0.162 mg. of creatinine (0.755 mg. from the recipient's kidneys) and 2.640 mg. of sodium chloride (1.485 mg. from the recipient's kidneys). The glomeruli and the tubules were normal. Albuminoid material was present in a few capsular spaces and tubules. There were numerous small areas of congestion, mononuclear cells and edema in the interstitial tissue. The capsule of the kidney showed extravasation, formation of fibrin, polymorphonuclear leukocytic infiltration and capillary proliferation.

At the end of forty-eight hours the urinary excretion was profuse. Each cubic centimeter contained 1.142 mg. of urea and ammonia nitrogen (26.667 mg. from the recipient's kidneys), 0.135 mg. of creatinine (1,250 mg. from the recipient's kidneys) and 4.455 mg. of sodium chloride (1.073 mg. from the recipient's kidneys). The glomeruli and the tubules were normal. Albuminoid material was present in a few capsular spaces and tubules. There were several collections of mononuclear cells, edema and diffuse congestion in the interstitial tissue. The capsule of the kidney showed extravasation, formation of fibrin, polymorphonuclear leukocytic infiltration, few newly formed capillaries and a proliferation of the fibroblasts.

At the end of seventy-two hours the urinary excretion was profuse. Each cubic centimeter contained 1.408 mg. of urea and ammonia nitrogen (24.990 mg. from the recipient's kidneys), 0.084 mg. of creatinine (0.760 mg. from the recipient's kidneys) and 4.538 mg. of sodium chloride (0.660 mg. from the recipient's kidneys). The glomeruli were normal. Granular degeneration of the epithelial cells was present in a number of tubules. The lumens of a few tubules were dilated. Albuminoid material was present in a few others. There were more and larger

collections of mononuclear cells and diffuse and marked congestion in the interstitial tissue. The capsule of the kidney showed extravasation, polymorphonuclear leukocytic infiltration, formation of new capillaries and active proliferation of the fibroblasts.

At the end of ninety-six hours the urinary excretion was scanty. Each cubic centimeter contained 1.428 mg. of urea and ammonia nitrogen (34.483 mg. from

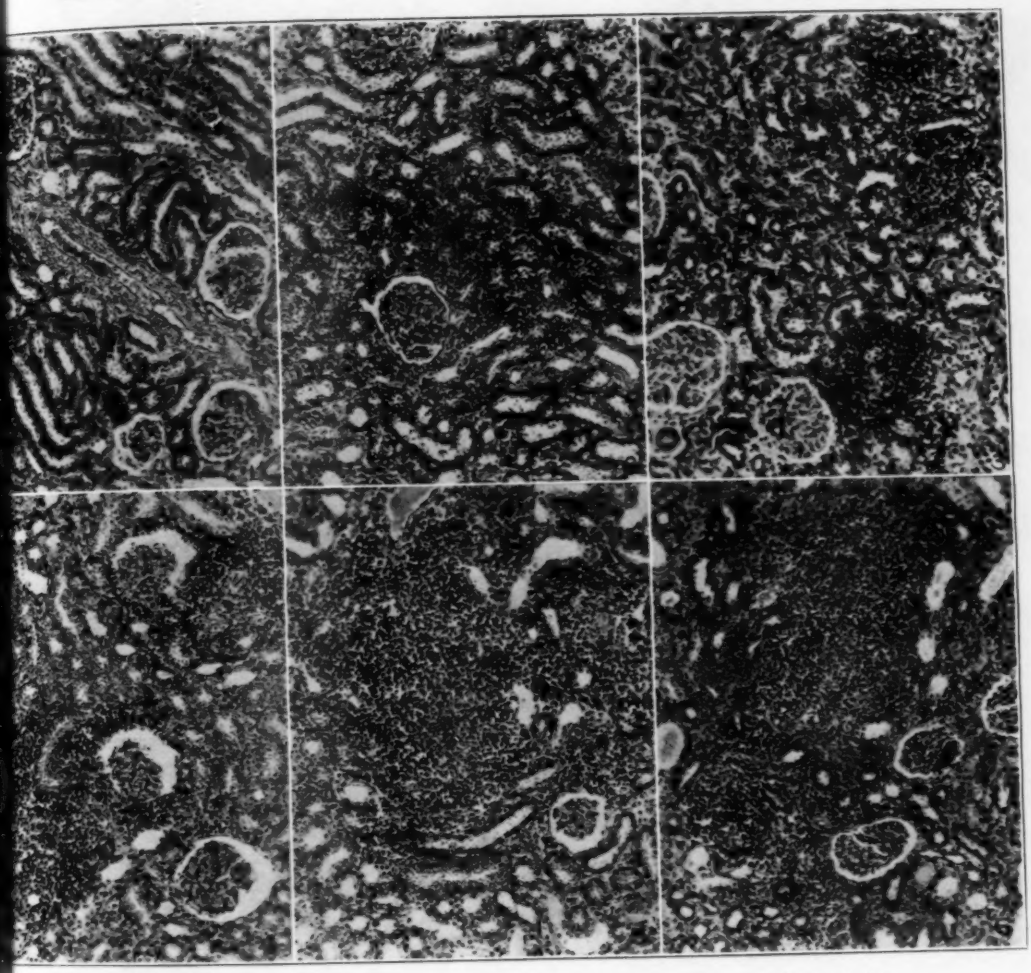

Fig. 2.—Histologic appearance of a functioning homogenous transplant of the kidney from day to day. The progressively more marked mononuclear cellular infiltration and the necrosis in the end may be noted (× 130).

the recipient's kidneys), 0.126 mg. of creatinine (1.379 mg. from the recipient's kidneys) and 6.436 mg. of sodium chloride (0.742 mg. from the recipient's kidneys). The glomeruli were normal. Many of the tubules were swollen, and there was granular degeneration of the epithelial cells. A few clusters of them were hyalinized. There was cystic dilatation of the lumens of a few

tubules and an albuminoid material in a few others. The interstitial tissue was markedly and diffusely congested with mononuclear cellular infiltration. The capsule of the kidney gave evidence of much organization and many fibroblasts.

At the end of one hundred and twenty hours the urinary excretion was scanty. Each cubic centimeter contained 0.571 mg. of urea and ammonia nitrogen (8.715 mg. from the recipient's kidneys), 0.161 mg. of creatinine (0.843 mg. from the recipient's kidneys) and 3,960 mg. of sodium chloride (0.907 mg. from the recipient's kidneys). The glomeruli were normal. A few clusters of tubules revealed swelling and granular degeneration of the epithelial cells. Many tubules showed a cystic dilatation of their lumens or contained albuminoid material. Extensive necrosis was associated with many mononuclear cells and a few areas of congestion. The capsule of the kidney showed much organization which extended for a certain distance into the renal substance.

At the end of one hundred and forty-four hours the transplanted kidney was removed at operation. It weighed 59 mg., measured 6.5 by 3.8 by 3.5 cm. and was markedly hydronephrotic. The normal kidney weighed 32 Gm. and measured 7 by 3.5 by 3 cm.

Nonfunctioning Homogenous Transplants: As a rule the glomeruli were normal. In one of the experiments, they were relatively bloodless on the first day; the capillary wall appeared to be thickened on the third day, and more cellular than usual on the fourth. In another experiment, albuminoid material was present in an occasional capsular space. The tubules generally manifested a progressively increasing amount of swelling and granular degeneration or hyalinization of the epithelial cells. However, they were sometimes normal in appearance from the beginning, or after showing some degenerative changes on the first day. Albuminoid material was found almost invariably to fill the lumens of a large number of tubules throughout the period of observation. Dilatation of the lumens of the tubules had been noted on the second and third days. The interstitial tissue always contained more and larger collections of mononuclear cells and areas of congestion each day. Necrosis was evident on the second day, and extensive on the third and the fourth days in some cases. The capsule of the kidney was practically normal or contained some extravasated blood and polymorphonuclear leukocytes on the first day. Organization began to take place on the second day and thenceforth became daily more advanced.

The illustrative protocol of experiment 14 (fig. 3) is as follows:

The recipient was an adult male spitz, weighing 8.2 Kg. The donor was an adult male spitz, weighing 11.5 Kg. Transplantation of a homogenous kidney was done on June 17, 1931, between 9 and 10:15 a. m. The circulation to the transplanted kidney was restored in thirty minutes. Excretion of urine was not noted at any time.

At the end of twenty-four hours the glomeruli were normal except that the capillary loops contained practically no blood corpuscles. The tubules were swollen,

and there was granular degeneration of the cytoplasm of the epithelial cells; the nuclei remained normal. The lumens of a large number of tubules were filled with albuminoid material. There was diffuse congestion of the interstitial tissue. The capsule of the kidney gave evidence of extravasation and polymorphonuclear leukocytic infiltration.

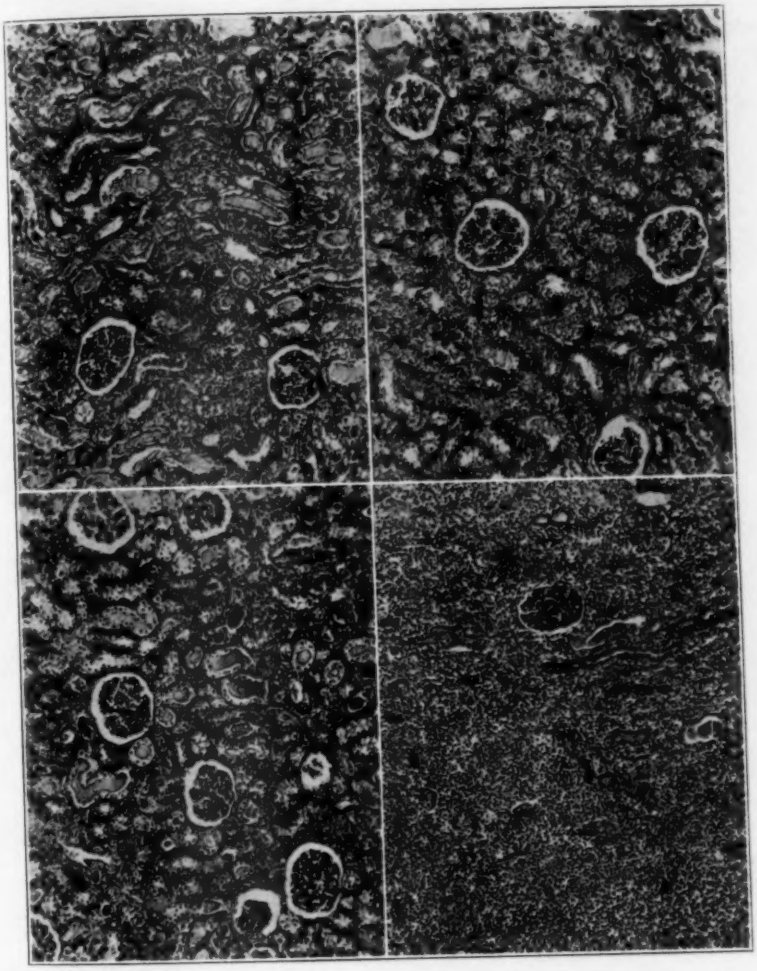

Fig. 3.—Histologic appearance of a nonfunctioning homogenous transplant of the kidney from day to day (× 130).

At the end of forty-eight hours the glomeruli and the tubules remained essentially the same. Albuminoid material was still present in a large number of tubules. The congestion in the interstitial tissue was more marked. The capsule of the kidney manifested polymorphonuclear leukocytic infiltration, formation of new capillaries, proliferation of the fibroblasts and an increased amount of fibrous tissue.

At the end of seventy-two hours the glomeruli appeared smaller than usual, and there seemed to be a relative thickening of the capillary walls. The tubules showed more swelling and granular degeneration and still contained an abundant amount of albuminoid material. There were a few small collections of mononuclear cells in addition to diffuse and marked congestion of the interstitial tissue. The capsule of the kidney showed more organization and fibrous thickening.

At the end of one hundred and twenty hours the glomeruli continued to appear smaller than usual. There seemed to be an increase in the number of cells, and the open capillary loops were not easily distinguishable. Most of the tubules were

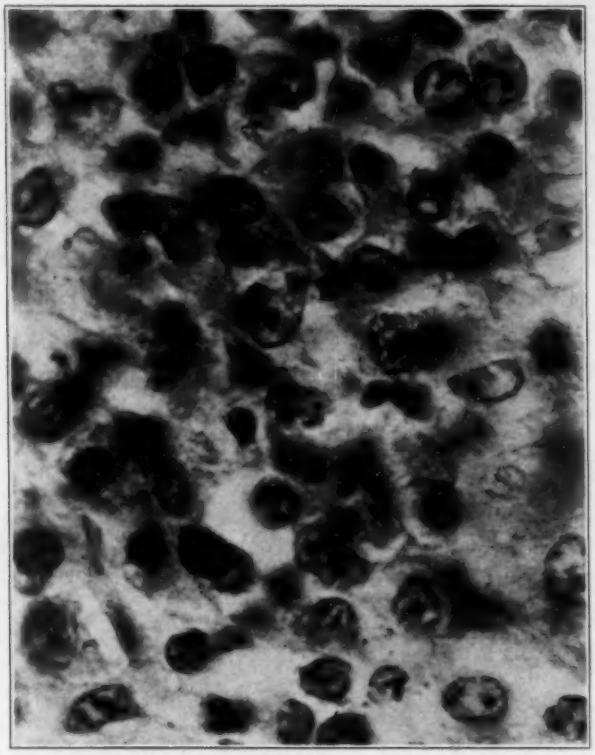

Fig. 4.—Characteristic mononuclear cells that were found to invade the transplants (× 1,400).

destroyed. Albuminoid material was present in the few remaining tubules. There were congestion and polymorphonuclear leukocytic infiltration of the interstitial tissue, with many large areas of necrosis. The capsule of the kidney showed still more organization and fibrosis than before.

At the end of one hundred and forty-four hours an exploratory operation revealed thrombosis in the renal vessels. The transplanted kidney was necrotic.

Summary of the Histologic Data: Comparatively speaking, such changes as were observed to be present or absent in the glomeruli and tubules are not distinctive of either the autogenous or the homogenous kidney transplant. In both cases, the glomeruli showed no

particular structural alteration. Occasionally there was albuminoid material in a few capsular spaces. The tubules appeared normal or exhibited a varying amount of degeneration, or a change from one to the other. The degeneration of the epithelial cells, principally of those lining the convoluted tubules and the thick limbs of the loops of Henle, usually consisted of swelling and granular changes in the cytoplasm with the nuclei remaining apparently intact. Hyalinization of the cells also occurred.

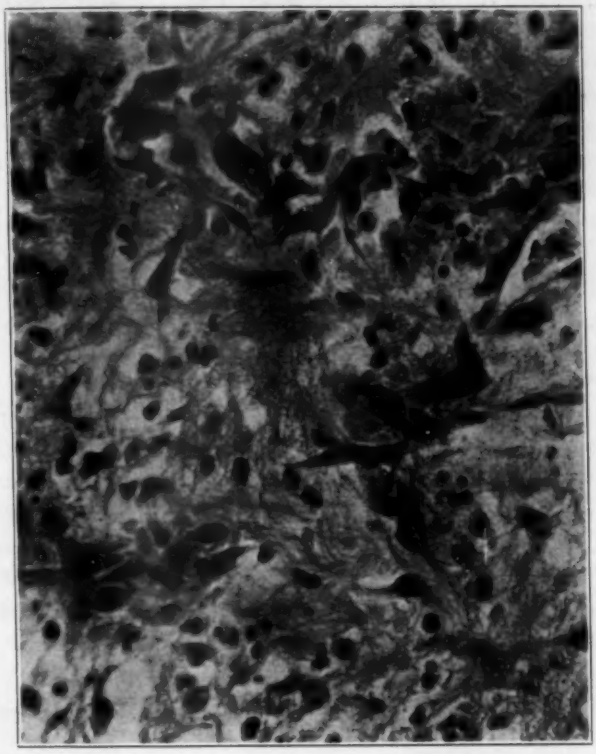

Fig. 5.—Active proliferation of fibroblasts noted in the capsules of the transplanted kidneys (× 500).

In the autogenous and the homogenous transplants the collecting tubules and the thin limbs of Henle generally contained albuminoid material. But the amount seemed to be the most abundant in those homotransplants that failed to excrete urine. More or less dilatation of the lumens of a varying number of tubules also took place.

Mononuclear cells were found to invade both varieties of transplants (fig. 4). Instead of showing a diffuse distribution, they appeared in the perivascular region as often as in collections without special reference to any of the structural components of the kidney. In the auto-

transplant they seemed to occur in numbers somewhat proportional to the amount of degeneration. Sometimes they were altogether absent. In the homotransplant, on the other hand, there was usually a progressively increasing number of these cells. Often the degree of infiltration did not correspond to the amount of degeneration. The kidney even appeared otherwise normal. In the course of time mononuclear cells overwhelmed the transplant and destroyed it.

Necrosis occurred in one variety of transplanted kidney as well as the other. Most of the time, it was associated with a number of polymorphonuclear leukocytes. In a few instances in the homotransplantation series, however, only mononuclear cells were present.

The capsule of the kidney always revealed a varying amount of extravasation, formation of fibrin and polymorphonuclear leukocytic infiltration on the first one or two days after the autotransplantation or homotransplantation. Then organization began and progressed actively. The amount of fibrous tissue was markedly increased in a short time (fig. 5).

COMMENT

The operation of transplantation involves an unavoidable amount of exposure and manipulation of the organ and disturbance of its blood supply. The kidney is injured, as evidenced by structural degeneration and functional impairment. For the same reason, the biopsy operation is also harmful, although to a much less degree. But, remarkably enough, a kidney that is subjected to such a procedure every day often tends to resume a normal histologic appearance and to be improved functionally. However, this holds true only for the autogenous transplanted kidney. It seems that, under the unfavorable conditions which arise after transplanting the organ of one subject into the body of another the homogenous transplant possesses a diminished power of resistance to injury or fails to recover rapidly from it.

In the transplantation of tissues in general, a few lymphocytes may be found here and there in an autotransplant in the first few weeks. Soon the small collections of lymphocytes begin to disappear until they are no more than those present in normal tissue.[16] In a homotransplant, however, after seven or eight days a remarkable infiltration by lymphocytes takes place; these surround and invade the living tissue. In the case of renal tissue in particular, lymphocytes are only occasionally present in the autotransplant. In the homotransplant, however, they are found at first around and in the peripheral zone of the living renal tissue.[16] Then the lymphocytes collect about the tubules in increasing

16. Loeb, Leo: Transplantation and Individuality, Physiol. Rev. **10**:547 (Oct.) 1930.

number and, after the tenth day, penetrate into the glomeruli and the lumens of the tubules.[17]

The mononuclear cells that have been found to invade the autogenous and homogenous transplants of the kidney are predominantly of the large mononuclear type and include relatively few lymphocytes. Probably the difference is one of terminology, and the same kind of cells are always involved in the reaction of the host to an autotransplant or a homotransplant.

It is to be expected that the cellular reaction should generally be evident as soon as the first or second day after transplanting the organ and rapidly increase in intensity. With an intact blood supply there is immediate and most intimate contact between the cells of the transplanted kidney and the fluids of the host.

Necrosis in areas of varying size was observed toward the end in several experiments. Usually it is associated with a large number of polymorphonuclear leukocytes. Sometimes only mononuclear cells are present. This may be the sequel of a mononuclear cellular infiltration, often extensive in the homotransplant, either directly or by interfering with the nourishment of the parenchyma. Then, as in the case of infarction, the invasion of the polymorphonuclear leukocytes is secondary to autolysis. But hydronephrosis and pyonephrosis are of frequent occurrence. A varying number of pus cells was invariably found in the urine. The urine was cultured twice, and both times the reaction was positive for Bacillus coli. Therefore, the pathologic picture probably represents pyelonephritis from an ascending infection of the urinary tract.

Thrombosis in the vessels at the site of anastomosis between the host and the transplant occurs more frequently after homotransplantation than after autotransplantation. However, this does not explain the peculiar functional behavior of the homogenous transplant of the kidney. Often when function has definitely failed, exploratory operations for several days afterward reveal the blood supply to be intact. Wounds in the kidney bleed profusely and heal well. Microscopic examination of specimens of the tissue removed at biopsy does not show thrombosis in the vessels or any sign of infarction. Instead of being the result of thrombosis, necrosis in the kidney often precedes it and seems to favor its occurrence.

The capsule of the kidney generally shows a marked increase in the amount of fibrous tissue. It probably exerts a constricting and injurious effect on the transplant by interfering with the blood supply and by preventing the change in the volume of the kidney which normally takes place.

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17. Loeb, Leo: Further Investigations on Auto and Homoioplastic Transplantation of Kidney Tissue. J. M. Research **37**:229 (Nov.) 1917.

Although the difference in functional behavior between an autogenous and a homogenous transplant of the kidney may be explained to a certain extent on a pathologico-anatomic basis, the underlying cause for the existence of the pathologico-anatomic difference remains to be designated. In the absence of any definite knowledge, biologic factors are generally held responsible.

Loeb [16] suggested that after transplanting an organ from one animal into another of the same species, a homodifferential develops. In the inadequate environment it assumes injurious properties, either directly or after interaction with the body fluids of the host, being thus transformed into a homotoxin. And it is this toxin which calls into play the reactions on the part of the host. Neuhof [18] believed that tissue compatibility or incompatibility lies at the root of the problem. The basis is probably physicochemical.

The present state of knowledge points to two separate channels through which improvement in the results of homotransplantation may be expected.

The first possibility of improvement consists in the proper selection of the host and the donor. This is suggested by the experience of Dederer.[19] He used puppies of the same litter, and a transplanted kidney functioned well continuously until the host died from intercurrent distemper twenty-six days later. According to Loeb,[16] this falls into the category of syngenesiotransplantation rather than homotransplantation.

The second possibility lies in the suppression of individuality. The reactions against homotransplants are due to the active metabolism of the homogenous tissues or to the presence of very labile substances.[16] Siebert [20] has shown that it is possible, through graded exposure of the homogenous tissue previous to transplantation, to find an intensity of heat which, while allowing the tissue to live and to regenerate, does not to any extent attract the lymphocytes of the host. It is obvious, of course, that unless the function of the kidney is preserved, such a procedure is not applicable.

Surgery as a mechanical craft is almost complete. Operations have been performed on every organ of the body. Although it cannot be said that every operation has been conceived, it is clear that no startling innovation in the realm of pure surgical handicraft is to be expected, except possibly in the direction of the transplantation of organs.[21]

18. Neuhof, Harold: The Transplantation of Tissues, New York, D. Appleton and Company, 1923, p. 297.

19. Dederer, Carleton: Successful Experimental Homotransplantation of the Kidney and the Ovary, Surg., Gynec., & Obst. **31**:45 (July) 1920.

20. Siebert, W. J.: Effect of Graded Degrees of Heat upon Cartilage on Homoiotransplantation and Heterotransplantation in Guinea Pig, Proc. Soc. Exper. Biol. & Med. **26**:238 (Nov. 27) 1928.

21. Ogilvie, W. H.: Recent Advances in Surgery, ed. 2, London, J. & A. Churchill, 1929, p. 495.

Transplantation of the kidney gives promise of clinical usefulness. The destruction of both kidneys from tuberculosis, corrosive mercuric chloride poisoning or any other condition constitutes an indication for such a procedure. Under those conditions there is no other choice in order to prolong or to save the life of the person.

The experiments in autotransplantation have proved conclusively that the kidney can be transplanted. In clinical surgery, however, there is practically no occasion for autotransplantation. Heterotransplantation has been performed several times with complete failure as the uniform result.[22] Homotransplantation remains to be attempted. The difficulty, of course, lies in obtaining a human kidney transplant. But, it is not an insurmountable obstacle in view of the fact that a person can live normally with a single kidney.

The species of animals commonly used in the laboratory cannot be arranged in groups comparable to the blood groups of man.[23] In the experiments on homotransplantation, it is therefore not possible to select the donor on the basis of compatibility of the blood. Loeb[16] believed that it is improbable that the blood group of host and donor can be of great significance in this connection, while Neuhof thought that blood compatibility should be a basis for satisfactory results. It remains to be seen whether the clinical application of this principle will produce results different from and better than those obtained thus far in experiments on animals.

On the basis of our present knowledge of the subject there can be only one conclusion. As emphasized by Mann,[24] the successful transplantation of a healthy organ to replace a diseased one awaits the discovery of the biologic factors which prevent the survival of the tissue of one subject when transplanted into the body of another, together with the development of methods to hold the action of these factors in abeyance.

SUMMARY AND CONCLUSIONS

The purpose of this study is twofold: to ascertain the histologic changes which may take place in the transplanted kidneys from one day to another, and to note if there is a difference—qualitative, quan-

22. Jaboulay, M.: Greffe de reins au pli du coude par soudures arterielles et veineuses, Lyon méd. **107**:575, 1906. Ullmann, Emerich: Experimentelle Nierentransplantation, Wien. klin. Wchnschr. **15**:281 (March 13) 1902. Unger, Ernst: Nierentransplantationen, Berl. klin. Wchnschr. **47**:573 (March 28) 1910. Neuhof.[18]

23. Sanford, A. H., and Mann, F. C.: Unpublished data. Neuhof.[18]

24. Mann, F. C.: Transplantation of Organs, in Contributions to Medical Sciences in Honor of Dr. Emanuel Libman by His Pupils, Friends and Colleagues, New York, The International Press, 1932. p. 757.

titative or in the sequence of events—between an autogenous and a homogenous transplant, as well as between a functioning and a nonfunctioning homotransplant.

Six autotransplantations and eighteen homotransplantations of the kidney were performed. Only five autotransplants and thirteen homotransplants were suitable for this study. Sixty biopsies were made. A total of one hundred and eighty histologic sections were examined.

Dogs were used for the experiments. The operations were performed under ether anesthesia and with sterile technic. The kidneys were transplanted by anastomosis of blood vessels into the neck. The functional capacity each day was estimated by the results of chemical analyses of the urine. The sequence of events in the histologic structures was followed by biopsies every twenty-four hours. The observations were limited to the first five days after transplantation.

All of the autogenous and six of the homogenous transplants functioned alike until the transplant was removed at operation, until the animal died or until thrombosis in one or both vessels or pyelonephritis occurred. One homotransplant excreted urine only part of the time, and six others failed to do so at any time during the period of observation. Thrombosis was not the cause of the failure to function, because in such cases exploratory operations revealed the vessels to be patent, and the biopsy wounds bled and healed as usual.

The autogenous and the homogenous transplants did not show distinctive changes in structure. In one as in the other, the glomeruli appeared normal, the tubules contained a varying amount of albuminoid material, dilatation or degeneration, and the capsule of the kidney had undergone organization and fibrosis. Quantitatively, however, in the case of the nonfunctioning homotransplants the tubules seemed to contain a greater amount of albuminoid material than usual.

Both varieties of transplants may show a few small collections of mononuclear cells on the first one or two days following transplantation. In the homotransplant, however, the infiltration is soon present in excess of the amount of degeneration and is followed by necrosis and destruction of the parenchyma. On the other hand, in the autotransplant, the number of those cells appears to be somewhat proportional to the severity and extent of the degenerative changes, and it tends either to remain the same or to diminish.

Although the course of changes that accrued from day to day was progressive in both cases, it seemed that in the autotransplant it was reparative, whereas in the homotransplant it was degenerative. No evidence was found to suggest the type of biologic factors which elicit the reaction between the host and the transplant after homotransplantation.

MEDIAL TORSION OF THE LEG

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Although volumes have been written about the deformities of the leg, almost no clinical attention has been given to torsional deformities of the developmental type. If the observations reported here are correct, these deformities not only bear a genuine academic interest but are of considerable clinical importance. In fact, one must give recognition to these deformities if one is to explain certain phenomena associated with lateral bowing of the legs which cannot be properly explained by the mechanics of a lateral bend. The torsional abnormality is likewise needed to account for the failure of standard therapeutic procedures in the correction of well known deformities of the feet.

The studies were made on patients seen in the clinic for rickets of the Johns Hopkins pediatric service. The clinic material includes nonrachitic children with abnormalities of gait and posture, as well as those with the rachitic caricatures of physiologic curves, who supply excellent material for the investigation of deformities of developmental origin. As one observed these children, one frequently noted the waddling gait and the intoe so generally associated with bowlegs. But the amount of waddling and toeing in was by no means uniformly proportionate to the amount of lateral bowing. Furthermore, the mechanics associated with an outward bow did not fully explain the gait. The effort to clarify these discrepancies directed attention to the medial torsion of the leg, a term used to describe an inward twist of the lower part of the leg when the knees are kept in their normal position; that is, when the upper part of the tibia and fibula is held in the normal position, the lower part is rotated on the longitudinal axis so that the normal anterior surfaces are medially displaced. This deformity involves only the portion between the knee and the ankle and does not include the irregularities of the foot and thigh.

The recognition of torsional displacement of a cylindric body without adequate surface markings is difficult. For the same reason an inward twist of the leg can easily escape the eye of the clinician. The cylindroid shape of the leg and the paucity of obvious prominences and reliable landmarks, as well as the mobility of both ends, make it easy to overlook this type of deformity. The apparent criterion, the crest

Read at the meeting of the American Orthopaedic Association, May 10, 1933.
From the Departments of Orthopedic Surgery and Paediatrics of the Johns Hopkins Medical School.

of the tibia, cannot be accepted as reliable because normally it slants inward and becomes indeterminate in the lower half of the tibia. The asymmetrical placement of the lower malleoli with regard to the transverse axis of the ankle makes it all the more difficult to recognize the alinement of the ankle joint. It is easy to see, therefore, how a moderate torsional deformity can escape the eye of the examiner unless specific details for the recognition are supplied.

In the normal limb the knee faces directly forward as the foot, anatomically placed with regard to the ankle, points forward. This position becomes the clinical zero point from which medial twists may be measured in degrees as apparent torsion. The measurement of apparent torsion or clinical torsion must be differentiated from the absolute readings available to anatomists. In the dissected specimen it is

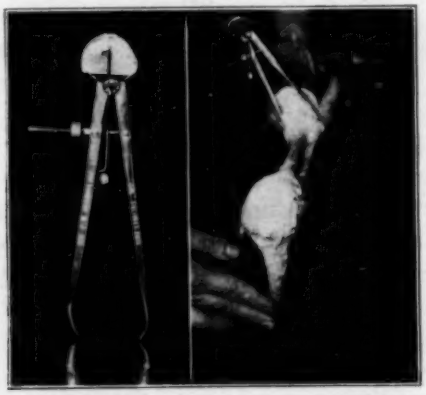

Fig. 1.—Torsionometer and method of use; the instrument consists of a caliper and pendulum with an indicator attached.

possible to measure the torsion of the leg accurately by projecting the transverse axis of the knee on the transverse axis of the ankle and reading the angulation. In fact, statistics are available that indicate that in the clinical normal there is an absolute average outward twist of 28.4 degrees.[1] It will be necessary, therefore, when the living patient is being considered to translate the absolute figures of the dissected leg into the apparent readings. Clinical readings may be made by supporting the foot in the normal right-angled relationship at the ankle, when the angle made by the foot with the anteroposterior axis of the knee can be estimated, or one may point the front of the knee directly upward and measure the torsion at the ankle with fair accuracy by the use of a simple caliper with a pendulum attached. More accurate measuring devices can be made, but they are cumbersome.

1. Strauss, William: Contrib. Embryol., 1927, vol. 19, no. 380.

ETIOLOGY

Bearing these criteria in mind, one finds medial torsion present in persons of all ages. In adults it is seen only occasionally. In children attending the clinic for rickets it is by no means an infrequent sight, while in the nursery of the department of obstetrics it is found in about 80 per cent of the new-born. Prehistoric man, as represented by reconstructions of the Cro-Magnon, La Ferrassie and Spy men, and, more particularly, the anthropoid apes likewise show this characteristic.[1] If one studies the available measurements, translated into the clinically apparent figures, one finds that inward torsion exists in the adult

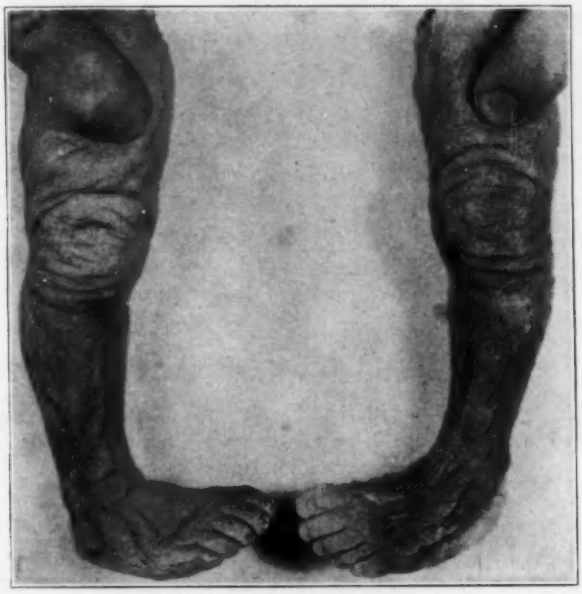

Fig. 2.—The amputated limbs of a new-born baby, demonstrating inward torsion of the legs.

orang-utan at 52 degrees; in the gorilla at 38 degrees; in prehistoric man at about 25 degrees; in the human 6 month fetus at 14 degrees; in the new-born at 17 degrees; in the juvenile at 11 degrees, and in the human adult at 0 degrees. From this one may deduce that our anthropologic ancestors began with an inward twist which has unwound itself phylogenetically and ontogenetically to produce the leg of the modern man. If this is true, one may consider atavistic reversion and developmental arrest etiologic factors for medial torsion. One might further expect that, as a rule, the unwinding process will have more opportunity to go on to its completion in the tall adult than in the person of stunted growth. Gross observations tend to substantiate this by revealing that

the inward twist is more prevalent in short people. It is likely that the unwinding takes place at the epiphyses rather than in the shaft, since (1) it acts during the period of growth, (2) it is evidenced in children who have for some reason or other never walked (this is a contradiction

Fig. 3.—A 2 year old rachitic child with torsion, showing outward facing of the patellas when the feet are in an approximately normal alinement.

Fig. 4.—Legs dissected to show abnormal alinement of the tibia and fibula in medial torsion.

of Le Damany's assumption that it results from bipedal locomotion), and (3) it manifests itself in children whose bones have been kept hardened by intensive medication with viosterol. Bone-softening diseases such as rickets permit an exaggeration of the normal curves by inter-

ference with epiphyseal development and by allowing the shafts to bow under a superincumbent weight. As in the spine, extensive lateral bowing will generally be accompanied by rotation. This concomitance of rotatory deformity with lateral bend can be demonstrated in the laboratory if one attempts to angulate the softened bones of the leg laterally. Pathologic factors, such as infantile paralysis, distal malformations and traumas, are not considered in this paper. Sex variations are found to be negligible, and the predominance of colored patients over white is probably due to the greater incidence of rickets in the former.

PATHOLOGIC ANATOMY

The normal adult tibia and fibula present the following important relations:

The fibula is lateral and posterior to the tibia in practically its entire length. The lower end of the fibula extends distal to the lower end of the tibial malleolus for a distance of approximately 1.5 cm. The transverse axis of the ankle cannot be established by the widest point between malleolar prominences. A more accurate gage, for clinical purposes, of the transverse axis of the ankle is one in which a line is drawn from the tip of the internal malleolus to the most prominent point on the anterior border of the lateral malleolus. The crest of the tibia does not supply a reliable landmark because in the lower half of the tibia it curves inward and loses its clearness. This fact is of importance because at first sight one might confuse the inward displacement of the crest with an inward twist of the leg. The fibula is normally articulated with the tibia at its proximal end with a true synovial membrane. There is a definite amount of mobility that can be obtained at this point in the dissected specimen. The lower tibiofibular articulation is much more firmly knit and does not present a clearcut synovial membrane. There is, nevertheless, an unmistakable amount of play available at this point. In the patient with inward torsion the fibula is carried forward by the tibial torsion so that the lower end of the fibula is not posterior, but anterior, to the bisecting frontal plane. Furthermore, a foreshortening of the fibula must take place, as it is spiraled around the tibia so that when the head of the fibula remains fixed the tip of the malleolus must be abnormally high. As a rule, in most of the patients with marked inward rotation the tip of the fibular malleolus is practically on a plane with the tip of the tibial malleolus.

CLINICAL PICTURE

In the symptomatology and the physical findings one meets factors of considerable practical interest. The child is usually brought in with

the complaint of bowlegs. Occasionally the maternal complaint is that "the child walks pigeon-toed." Not infrequently a patient is referred because he is believed to have rickets, though he fails to show rachitic changes on clinical or roentgen examination. The primary picture is as follows:

1. It is noticed that an apparently healthy baby, possibly somewhat overweight but certainly quite active, walks with a marked inward pointing of the feet. If the child is allowed to stand, one finds no evidence of metatarsus varus or hallux varus. The foot is well balanced in its relation to the lower part of the leg. Frequently there is a pronounced lateral bow. If the patient is allowed to sit with the feet suspended over the edge of the table and the knees together, it is found that the feet point inward. This is particularly emphasized by the appearance of the extremity when the physician supports the foot with the ankle in the normal position. If the legs are stretched out on the table so that a line dropped through the prominence of the tibial tuberosity forms a perpendicular with the table, the lower part of the leg will be definitely twisted inward. While the aforementioned instrument proves of assistance in recording the amount of twist, it is not necessary for gross recognition of the deformity. It is noteworthy that the abnormal gait is much more pronounced when the patient is actually walking than when he is standing still.

2. Again, many patients present themselves because of bowlegs. When the patient is allowed to lie on the table and the feet are apposed, however, no gross lateral bowing is observed. This observation was particularly brought forth during the recently prevailing fashion for knee-length skirts. Young women seeking assistance for what appeared to them cosmetic deficiency not infrequently failed to find sympathy in the attending physician because of this apparent lack of separation between the inner aspects of the limbs when the feet were apposed. On the other hand, in patients of this type one finds that the alinement of the feet has been accomplished by the relative external rotation of the limbs at the hips, with the result that the normal posterior fulness of the calf is displaced toward the midline so as to obscure the distance between the inner borders of the leg. The patient, however, is fully aware of the distortion, because when she assumes her normal gait the deformity becomes apparent. In patients of this sort, if the examining physician looks for the patellas when the feet are held together, he finds that they are facing distinctly outward. In an attempt to correct the awkward toeing in, the patient may of his own accord follow one (or both) of two courses: (1) eversion of the entire limb at the hip or (2) abduction of the foot at the mediotarsal joint.

3. The first of these compensatory maneuvers is responsible for another clinical manifestation, the bow-legged waddle. The gait is characteristic. There is a swaying of the trunk from the midline as each step is taken. It is not a shuffle such as one finds in the child with knock knee. At each step the trunk is swung onto the sustaining limb. The gait is not unlike that seen in patients with paresis of the gluteus medius and minimus muscles. Utilizing this comparison, one finds that the child who externally rotates the entire leg to compensate for the inward pointing of the foot impairs the function of the lesser glutei. The effect of the movement is to approximate the origin and insertion of the abductors of the leg, that is, the gluteus medius and minimus muscles. This results in a diminished function of the muscles so that assistance must be given to them by tilting the trunk to bring the center of gravity more nearly over the femoral head. Examinations of articulated skeletons as well as of normal adults indicate that an external rotation of 40 degrees shortens the distance between the greater trochanter and the approximate center of action of the gluteus medius and minimus muscles by from 1.5 to 2 cm., or by approximately 10 per cent of the normal distance. Care must be taken to rule out coxa vara.

4. The second compensatory maneuver, abduction of the foot at the mediotarsal joint so that the front part of the foot bears the normal walking alinement while the posterior portion retains the inward twist, gives one the fourth clinical anomaly. This abduction produces talipes valgus and the patient appears for treatment for flatfoot. It is not uncommon to find that children who stand with abduction of the foot walk with a marked varus gait, the so-called paradoxical clubfoot. The explanation for this paradox on the basis of the strain-relieving muscular pull when the child is walking is inadequate for all cases. Many of the children walk with an exaggerated toeing in, in spite of a mechanical support supplied to relieve the foot strain. On the other hand, the inward twist of the leg affords an explanation for the pigeon-toe gait in the presence of static valgus.

ROENTGENOGRAPHIC OBSERVATIONS

Most of the studies to which the patients were submitted required roentgenograms. It was natural, therefore, that one should expect reports of torsional deformities from the roentgenographic department. Since reports of this type were not forthcoming, an attempt was made to determine some roentgenologic corroboration of the clinical impressions. Unless one looks for certain specific factors, one may easily pass by many of the roentgenograms as showing no abnormalities.

To establish differential factors, roentgenograms were taken of a normal tibia and fibula. It was found that under the standard methods of exposure the shadow of the entire fibula lay beside the shadow of the tibia without overlapping. This was noted on both anteroposterior and lateral views. If, then, the bones were softened and an experimental torsion of 30, 60 or 90 degrees was made in the bones of the leg, the roentgenograms demonstrated an overlapping of the distal portions of the bones when the proximal portions were held in their normal relationship. A check-up between the clinical notes and the roentgen readings on my patients showed definite qualitative and quantitative

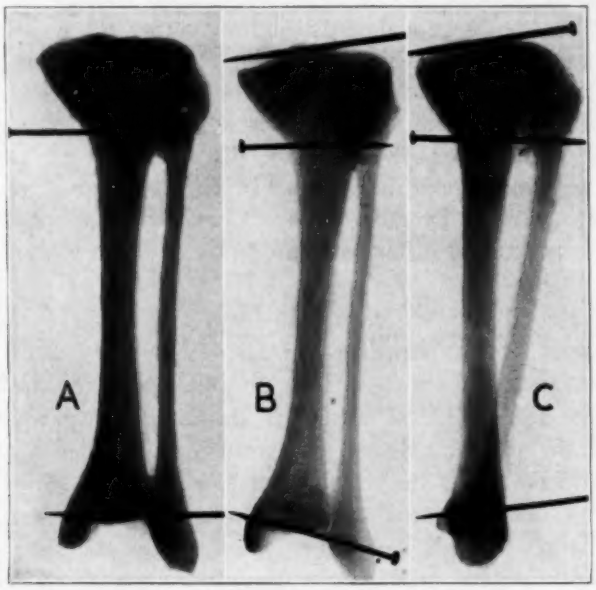

Fig. 5.—Roentgenogram of the decalcified bones of the leg showing: *A*, normal roentgen alinement of the tibia and fibula; *B*, experimental torsion of 30 degrees, when the fibular head overlaps the tibial head while the malleoli are in normal relationship, and *C*, experimental torsion of 90 degrees with the heads of the bone in a conventional roentgen position showing overlapping of the lower portions of the bones.

conformity. The amount of overlapping of the distal portions of the bones can be used to determine approximately the degree of deformity. Thus, if the shadow of the fibular malleolus covers half of the tibial expansion, a deformity of 45 degrees may be expected.

DIFFERENTIAL DIAGNOSIS

From the foregoing comment it must be apparent that in the differential diagnosis one must be careful not to confuse the condition with

hallux varus, metatarsus varus, traumatic torsional displacement and congenital dislocation of the hip. Coxa vara may produce a waddle, but it will usually have an associated restriction of abduction. Care should be taken not to confuse the inward swing of the crest of the tibia with true rotational distortion of the leg.

Fig. 6.—Roentgenogram of a leg with medial torsion of 45 degrees, showing superimposition of malleolar shadows when the upper ends are conventionally placed.

TREATMENT

The therapeutic measures involved are rather obvious. External rotatory maneuvers are desirable, but should be limited to the leg proper. Repeated manipulations at frequent intervals to unwind the bones of the leg are thus of considerable assistance in early childhood. The bowleg brace described by Bradford and Lovett, which allows control of rotation of the limb through an extension above the hip, is valuable in somewhat older patients. The osteotomies, particularly those described

by Peabody,[2] will be found necessary in adults and older children. It must be emphasized that the elevation of the inner border of the heel and sole in the child with flatfoot resulting from inward twisting, while beneficial to the alinement of the foot, is not likely to assist in the recovery of the torsional deformity. Any corrective measure which changes the weight-bearing surface of the shoes involves the undesirable factor of loss of efficiency through the rather mobile ankle joint. As in the therapeusis of ordinary bowleg, the earlier treatment is begun, the more easily correction of the deformity is accomplished.

Fig. 7.—Anteroposterior roentgenogram of the legs of the child in figure 3. The overlapping shadows of the heads of the bones is to be noted, though the lower ends are in the usual alinement.

SUMMARY

1. Attention is called to the existence of medial torsion of the leg of sufficient degree to be of clinical importance.

2. The deformity is not necessarily rachitic in origin. Evidence is presented to indicate that it is of developmental origin, and that it persists because of a developmental arrest, possibly exaggerated by postnatal factors.

2. Peabody, C. W.: J. Bone & Joint Surg. **14**:822 (Oct.) 1932.

3. Of the clinical manifestations, the more important are the toeing in and the waddling gait. The mechanics of this deformity afford a rational explanation for these symptoms.

4. It is possible to recognize the deformity by the roentgenographic criteria enumerated, but measurement of the clinical torsion is best made by the simple instrument described.

5. It is important to direct treatment to the leg rather than to the foot.

Dr. Edwards A. Park permitted us to use the material of the Harriet Lane Home, and Dr. David Shelling and Miss Katherine Hopper assisted with the clinical examinations and measurements.

SYMPATHETIC GANGLIONS REMOVED SURGICALLY

A HISTOPATHOLOGIC STUDY

ALBERT KUNTZ, PH.D., M.D.
ST. LOUIS

The results of sympathetic ganglionectomy in the surgical treatment of disease in many cases strongly suggest that dysfunction of the autonomic nerves is a factor in the disease process in question. The basic causes of the autonomic dysfunction, however, are not as yet fully understood. Lesions of the autonomic ganglions and ganglion cells doubtless must be regarded as important factors in many cases, but our knowledge of these lesions and their functional significance is fragmentary and incomplete.

REVIEW OF THE LITERATURE

Most of the data available at present regarding lesions of the autonomic ganglions and ganglion cells represent the results of histopathologic studies of preparations of ganglions obtained at autopsy following death due to a wide variety of causes. The earlier studies of this character, the results of which have been published, have been reviewed by Stämmler [1] (1923), who also reported the results of his own studies of ganglions obtained at autopsy in a large series of cases. On the basis of this review and the results of his own studies, Stämmler concluded that infectious disease usually is accompanied by pathologic changes in the autonomic ganglions and in many of the ganglion cells. In cases of acute infectious disease, the autonomic ganglions commonly become hyperemic and infiltrated with wandering cells, and the ganglion cells undergo degeneration in a greater or lesser degree. The infiltrating cells are mainly lymphocytes and mononuclear leukocytes which appear in large numbers in the perivascular lymphatics, but also invade the connective tissue and, in many instances, the ganglion cell capsules. The earliest recognizable changes in the ganglion cells, according to Stämmler, consist in enlargement of the nucleus and an apparent reduction in the quantity of intranuclear chromatin. The nuclear membrane also becomes thinner and less distinct, and the nucleolus may disappear. If the nucleus remains intact, it may maintain its normal position in the

From the St. Louis University School of Medicine.

1. Stämmler, M.: Zur Pathologie des sympathischen Nervensystems; im besonderen über seine Bedeutung für die Entstehung der Arteriosklerose, Beitr. z. path. Anat. u. z. allg. Path. **71**:388, 1923.

cell or become displaced into an eccentric position. Later, it may undergo reduction in size and become pyknotic. In the latter condition, it also exhibits a more intense staining reaction than does the normal nucleus. The earliest reaction of the cytoplasm involves swelling and a reduction in the intensity of its staining reaction. With the reduction in the size of the nucleus, the cytoplasm also undergoes a reduction in volume. In many ganglion cells, the initial changes are followed by atrophy leading to necrosis.

In cases of chronic infectious disease and other chronic pathologic states, particularly in older persons, as observed by most of the earlier investigators, the autonomic ganglions also exhibit a marked increase in the interstitial connective tissue. The chromidial content of many of the ganglion cells is diminished, and many of them contain melanotic pigment. The capsules of some of the ganglion cells also become thickened, and the capsule cells undergo proliferation.

The results of Mogilnitzky's [2] (1923, 1924 and 1927) studies on the histopathologic changes in the autonomic ganglions in cases of infectious disease in general corroborate those of Stämmler. Both of the investigators pointed out that the lesions observed in the autonomic ganglions are nonspecific and probably bear no direct relationship to the etiology of the disease in question.

The studies based on preparations of sympathetic ganglions removed surgically in the treatment of disease, the results of which have been published, also failed to reveal lesions in the ganglions or ganglion cells which could be regarded as directly related to the disease in question. In preparations of the cervical sympathetic ganglions removed by operation in a limited series of cases of Raynaud's disease and angina pectoris, Stämmler [3] (1924) described changes comparable to those observed in preparations of the autonomic ganglions in cases of chronic infectious disease. Clark [4] (1927) also observed no histopathologic changes which could be correlated with angina pectoris in preparations of the superior cervical sympathetic ganglions removed by operation in seven cases of the disease. Craig and Kernohan [5] (1933), who recently reported their

2. Mogilnitzky, B.: Die Veränderungen der sympathischen Ganglien bei Infektionskrankheiten, Virchows Arch. f. path. Anat. **241**:298, 1923; Die pathologische Anatomie des vegetativen Nervensystems beim Recurrens, ibid. **248**:137, 1924; Die pathologische Anatomie des vegetativen Nervensystems bei Malaria, ibid. **263**:839, 1927.

3. Stämmler, M.: Anatomische Befunde am sympathischen Nervensystem; Vasomotorische Neurosen, Deutsche med. Wchnschr. **50**:457, 1924.

4. Clark, S. L.: The Superior Cervical Sympathetic Ganglion in Angina Pectoris; a Microscopic Study, J. Lab. & Clin. Med. **13**:101, 1927.

5. Craig, W. McK., and Kernohan, J. W.: The Surgical Removal and Histologic Studies of Sympathetic Ganglia in Raynaud's Disease, Thrombo-Angiitis Obliterans, Chronic Infectious Arthritis, and Scleroderma, Surg., Gynec. & Obst. **56**:767, 1933.

findings in preparations of the sympathetic ganglions removed by operation in an extensive series of cases, including Raynaud's disease, thrombo-angiitis obliterans, chronic infectious arthritis and scleroderma, observed no significant histologic differences between the ganglions removed from patients with the various diseases and expressed the opinion that the changes present do not deviate beyond the normal limits, and that most of them can be explained on the basis of advancing age.

MATERIAL AND METHODS

The present study is based on preparations of sympathetic ganglions removed surgically from thirty patients, including nineteen with chronic polyarthritis, two with Raynaud's disease, two with thrombo-angiitis obliterans, one with endarteritis, one with spastic hemiplegia, one with progressive muscular dystrophy, one with adenothyrotoxicosis, one with pruritus ani and pruritus vulvi and one with congenital megacolon. The patient with congenital megacolon was 6, the one with spastic hemiplegia, 7, and the one with progressive muscular dystrophy, 11 years of age. The others ranged from 18 to 69. Of these, twenty-two were patients of Dr. W. T. Coughlin and eight, patients of Dr. J. F. Clancy, to both of whom I am indebted for the ganglions removed and the essential data contained in the cases reported here.

All of the ganglions were fixed in formaldehyde. Most of the preparations used were stained with toluidine blue and erythrosin; the rest, with cresyl violet. In addition to the preparations of the ganglions removed in the surgical treatment of disease, preparations of human sympathetic ganglions obtained at autopsy and sympathetic ganglions obtained from normal animals were available for comparative study.

As has been pointed out in the review of the literature, most of the earlier investigators who studied human autonomic ganglions obtained at autopsy, regardless of the causes of death, in a great majority of the cases observed histologic changes in the ganglions which they regarded as pathologic in slight degree. Our own studies of preparations of human autonomic ganglions obtained at autopsy following death due to a wide variety of causes in nearly every instance revealed conditions which, in comparison with the conditions observed in preparations of the ganglions of laboratory animals, cannot be regarded as normal. It has not been regarded as advantageous, therefore, to attempt to establish a norm, on the basis of human material, with which to compare the findings in the preparations of the sympathetic ganglion removed by operation. For the purposes of the present study, the autonomic ganglions of vigorous laboratory animals (cats) have been regarded as more nearly normal than the available human material obtained at autopsy.

HISTOPATHOLOGIC OBSERVATIONS

In the series under discussion, the preparations of sympathetic ganglions removed surgically, as compared with preparations of the ganglions of normal animals, with few exceptions, probably deviated from the range of normal variation in certain particulars. In most cases, they exhibited changes which have not been observed in preparations of the ganglions of normal animals. These changes varied in intensity within relatively wide limits in different individuals, but belonged to the same categories; consequently, they could not be regarded as specific for the disease in question in any case.

Preparations of all of the ganglions removed surgically in the series exhibited infiltration in some degree of the interstitial connective tissue with wandering cells, mainly lymphocytes and mononuclear leukocytes. The preparations of some of the ganglions, particularly those of the older patients, also exhibited hyperplasia of the interstitial connective tissue. The wandering cells present in the interstitial connective tissue stood out prominently in preparations of the ganglions by reason of the intense staining reaction of their nuclei (fig. 1 *B* and *C*). In the preparations of some of the ganglions the cells were present in small numbers and occurred either in groups or widely scattered in the interstitial tissue. In those of other ganglions lymphocytes and mononuclear leukocytes were present in larger numbers throughout the interstitial tissue. In four cases, they were observed to be particularly abundant around some of the smaller blood vessels (fig. 2), where many of them lay within the perivascular lymphatics.

In many instances cells apparently identical with the wandering cells in the interstitial tissue were present within the ganglion cell capsules. Some of these

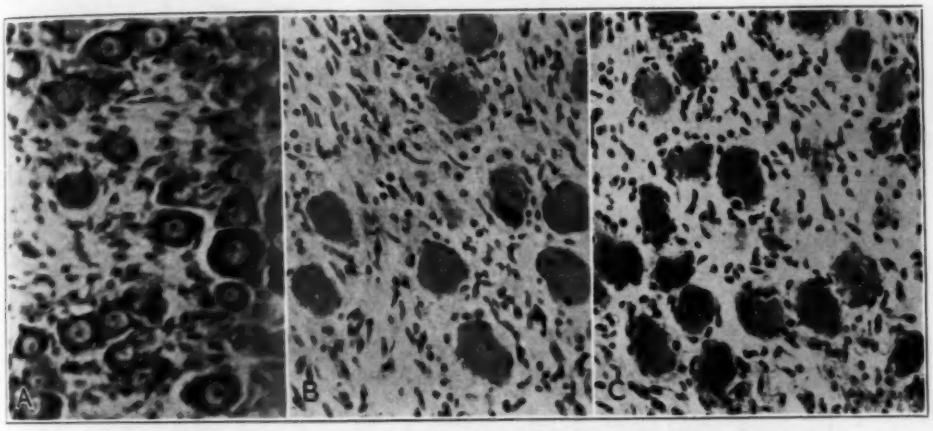

Fig. 1.—*A*, photomicrograph of a section of the sympathetic ganglion of a normal animal (cat); *B*, photomicrograph of a section of the cervical sympathetic ganglion removed surgically from a patient, 11 years of age, with progressive muscular dystrophy, showing infiltration with wandering cells; *C*, photomicrograph of a section of the lumbar sympathetic ganglion removed surgically from a patient with chronic polyarthritis, showing hyperplasia of the interstitial connective tissue and infiltration with wandering cells.

probably were wandering cells which had invaded the capsules; others probably arose owing to the proliferation of capsule cells. Some of the preparations also afforded evidence of proliferation of reticulo-endothelial cells in areas adjacent to the ganglion cell capsules.

In the interstitial tissue the relatively large caliber of many of the capillaries and small veins, partially or completely filled with blood cells, suggested hyperemia of the ganglions. This condition was possibly due in part to manipulation of the ganglion during the operative procedure. The fact, however, that sympathetic ganglions which were removed at autopsy and which exhibited evidence of chronic inflammation also were hyperemic favored the assumption that the hyperemia apparent in the ganglions in our series was related to other changes

in the ganglions. Not infrequently, aggregates of polymorphonuclear leukocytes appeared in contact with the endothelium of the vessels containing blood cells. In some of the cases, eosinophils made up a relatively high percentage of the cells.

In approximately one third of the cases some of the small arteries and veins in the ganglions exhibited marked thickening of the walls (fig. 3). The thickening

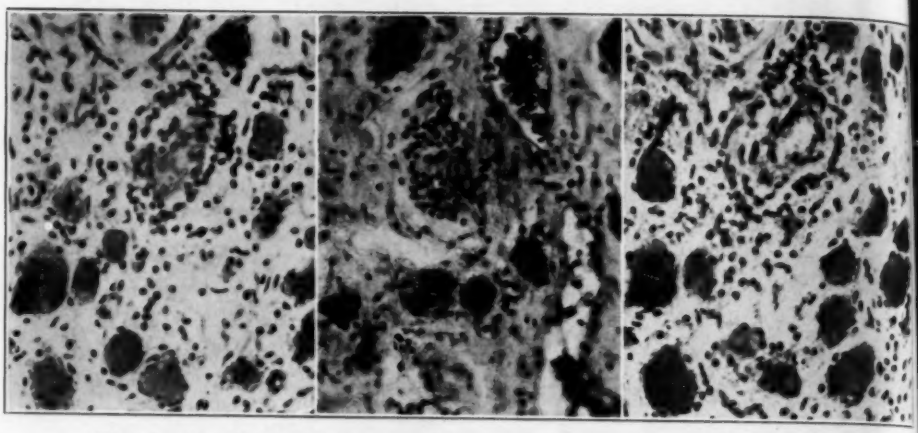

Fig. 2.—Photomicrographs of sections of the sympathetic ganglions removed surgically from patients with chronic polyarthritis, showing aggregations of wandering cells around small blood vessels.

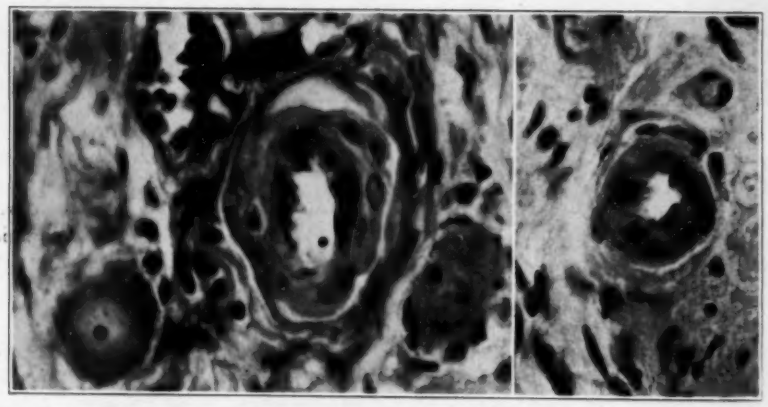

Fig. 3.—Photomicrographs of sections of sympathetic ganglions removed surgically from patients with chronic polyarthritis, showing thickening of the walls of the small arteries.

was brought about in part by hyperplasia of the cellular elements, but in a larger measure by hypertrophy of the fibrous elements. In some of the ganglions, many of the smaller vessels, particularly small arteries and arterioles, also exhibited proliferation of the endothelium lining the intima. In some instances, invading white cells also were present in the vessel walls.

The changes in the ganglion cells included swelling and shrinking of the nucleus and cytoplasm, increase and diminution in the chromatin content of the nucleus and in the chromidial substance in the cytoplasm, pigmentation, vacuolation, hyaline degeneration and destruction by phagocytes.

Nearly all of the preparations in the present series contained some ganglion cells which were definitely swollen (fig. 4). The cells were in some instances enlarged to two or three times their normal size. They were present in only small numbers, except in the more pathologic ganglions. For example, the preparations of the ganglions of one of the patients with polyarthritis (arthritis deformans) exhibited swollen ganglion cells in large numbers. The preparations also exhibited numerous shrunken hyperchromatic ganglion cells as well as ganglion cells which had undergone no marked changes in volume but which contained a relatively meager supply of chromidial substance. The swelling and the shrunken hyperchromatic condition of the ganglion cells in this case were obviously not directly related to the arthritis, but were probably related to other pathologic processes, of which the record of this case affords evidence. In some of the swollen cells, the nucleus appeared abnormally large and vesicular and reacted

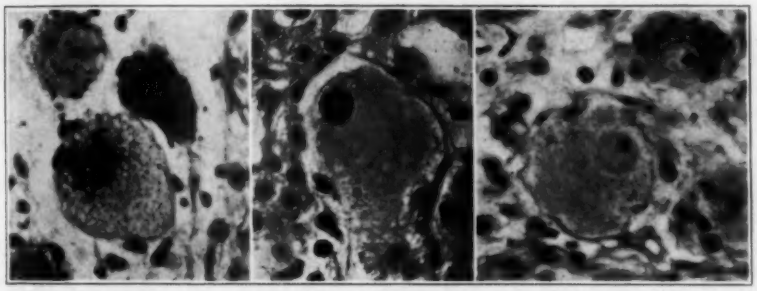

Fig. 4.—Photomicrographs of sections of sympathetic ganglions removed surgically from patients more than 50 years of age with chronic polyarthritis, showing swollen ganglion cells.

but lightly to the stain. In others, the nucleus was somewhat shrunken, slightly irregular in outline and reacted more or less intensely to the acid stain. The cytoplasmic body was so large that it completely filled the cell capsule, causing the latter to be considerably distended and reduced in thickness. Some of these swollen ganglion cells exhibited a narrow perinuclear zone in which there remained some chromidial substance, while the peripheral zone was devoid of this substance. Others exhibited only traces of chromidial substance in the cytoplasm. In the latter cells, the cytoplasm appeared finely granular and almost colorless.

The preparations of all the ganglions in the series exhibited some ganglion cells which were definitely shrunken and hyperchromatic. This condition was illustrated by the more intensely stained ganglion cells in figs. 1 *C* and 2 *B*. The chromidial substance in the cytoplasm, although abundant, did not appear in discrete chromidial bodies but in fine granules or in solution. In erythrosin-toluidine blue preparations, the cytoplasm assumed a diffuse blue or reddish color, depending on the degree of change which had taken place. The nuclei of many of the ganglion cells in this condition reacted intensely to the acid stain; those of others exhibited an excess of chromatin. Ganglion cells in this condition were present in relatively small numbers in the preparations of most of the ganglions.

Preparations of the ganglions of several patients, however, exhibited shrunken hyperchromatic ganglion cells in relatively large numbers. Of these, one was a patient, aged 11 years, with progressive muscular dystrophy; another, a patient 46 years of age, with paralysis agitans; another, the patient with arthritis deformans referred to earlier. The last patient was 52 years of age. The preparations of the ganglions of this last patient also exhibited numerous swollen ganglion cells.

Preparations of all the ganglions in the present series also exhibited some ganglion cells in which a portion of the cytoplasmic body was completely or almost completely devoid of chromidial substance and showed evidence of hyaline degeneration. In most of the cells, the nucleus was situated in an eccentric position at the periphery of the hyaline area. In most of the preparations, ganglion cells in this condition were present in only small numbers. In others, particularly those in which shrunken hyperchromatic ganglion cells were numerous, they were present in considerable abundance. These preparations also exhibited ganglion cells which probably represented intermediate stages between the shrunken hyperchromatic cells and those which showed frank hyaline degeneration. Ganglion cells which seemed to be undergoing hyaline degeneration were particularly abundant in the preparations of the ganglions of the patient with endarteritis. This patient was 44 years of age and gave a history of alcoholism and addiction to drugs.

One of the most uniform deviations from the condition of the majority of the ganglion cells in preparations of the ganglions of normal animals observed in the series of preparations was a reduction in the size of the chromidial bodies and in the quantity of the chromidial substances in the cytoplasm. In most of the ganglions used in this study, the chromidial substance was relatively meager in the great majority of the ganglion cells. The chromidial substance present in these cells existed in minute granules or in the form of chromidial dust. In the cells in which the chromidial substance was present in greater abundance, it commonly existed in the form of discrete chromidial bodies similar to those present in the ganglion cells of normal animals. The chromidial substance may be distributed more or less uniformly throughout the cytoplasm, or it may be concentrated mainly in either the perinuclear or the peripheral zone. The latter condition was most common in our preparations. Most of the ganglion cells which contained little chromidial substance in the cytoplasm also exhibited some diminution in the size of the nucleus and in the quantity of intranuclear chromatin.

Accumulations of pigment granules in the cytoplasm of many of the ganglion cells could be observed in the preparations of all the ganglions in the series, except those of the two youngest patients, who were 6 and 7 years of age, respectively. In some of the ganglions, relatively few ganglion cells were pigmented, and most of these only slightly. In others, pigment was present in nearly all of the ganglion cells, many of them being heavily pigmented. The pigment existed in dark granules of unequal size. In some cells, the pigment granules were scattered in small aggregates throughout the cytoplasm (fig. 5 *A* and *B*); in others, they constituted heavy, dark masses near the periphery of the cell body (fig. 5 *C*).

As previously stated, cells which probably were phagocytic were present within the capsules of some of the ganglion cells. In some of the ganglions, these cells were present in only a few of the ganglion cell capsules and only in small numbers; in others, they were present within the capsules of many of the ganglion cells. In many instances, the ganglion cell capsules were markedly thickened and the numbers of cells lining them were increased.

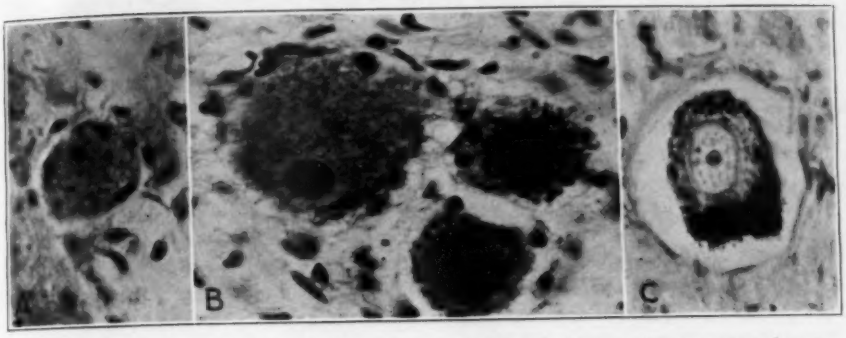

Fig. 5.—Photomicrographs of sections of sympathetic ganglions removed surgically, showing pigmented ganglion cells. In *A* and *B*, the pigment granules are in small aggregates throughout the cytoplasm; in *C*, they constitute heavy, dark masses near the periphery of the cell body.

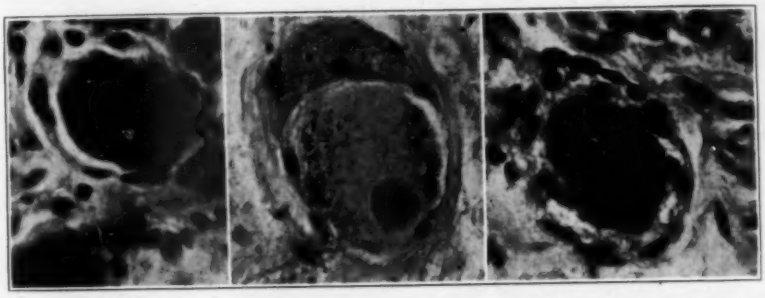

Fig. 6.—Photomicrographs of sections of sympathetic ganglions removed surgically, showing thickening of the ganglion cell capsules.

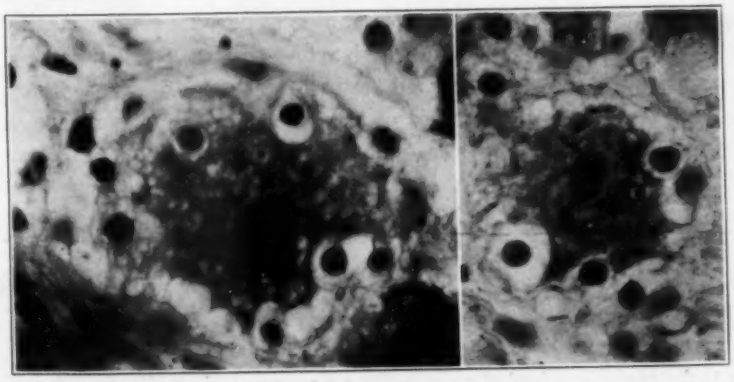

Fig. 7.—Photomicrographs of sections of sympathetic ganglions removed surgically, showing advanced neuronophagia.

The thickening of the capsule involved mainly its noncellular membranous portion in contact with which the endothelial cells lining the capsule rested (fig. 6). The latter cells normally constituted a single layer. In some of the thickened capsules, the endothelial cells had increased in number, and some of them no longer lay in direct contact with the membranous layer of the capsule. Some of the cells within the capsules probably represented endothelial elements which had become separated from the lining of the capsule; others, doubtless, had invaded the capsules from the interstitial tissue. The cells within a capsule gradually encroached on the ganglion cell and apparently consumed its cytoplasm (fig. 7). This phenomenon could be observed in nearly all of the preparations in the series but was most apparent in those of the ganglions of the older patients. In these ganglions, free cells were present within the capsules of a relatively large percentage of the ganglion cells. Most of the ganglion cells showed little destruction of cytoplasm; others exhibited consumption of the major portion of it. Ganglion cells in the latter condition also appeared necrotic.

COMMENT

The histopathologic changes in the sympathetic ganglions and ganglion cells already described fall into the same general categories as those described by earlier investigators, particularly Stämmler (1923 and 1924) and Mogilnitzky (1923 to 1927), in material obtained at autopsy in cases of infectious disease and in ganglions removed surgically in cases of Raynaud's disease and angina pectoris. The observations of Craig and Kernohan (1933) in the most extensive series of sympathetic ganglions removed surgically which has been available for study also fall into these categories, but these investigators regarded the changes observed as within the limits of normal variation. In comparing their observations with those of the earlier investigators already named and those set forth in this paper, it is significant to note that the criterion of the normal histologic structure of sympathetic ganglions used by them is based on a study of sympathetic ganglions obtained at autopsy in forty consecutive cases following death due to various causes. Although none of these patients had suffered from any of the conditions for which ganglionectomy had been done in their surgical series, no cognizance seems to have been taken of possible histopathologic changes in the ganglions which might be correlated with other pathologic processes. A norm established in this manner obviously represents a much wider range of variation than one based on a study of the ganglions of normal animals.

The histologic changes in many of my preparations conformed closely to those described by Craig and Kernohan. The preparations of some of the ganglions in the series, however, exhibited changes which seem to be more marked than were the corresponding changes described by these two investigators. For example, the interstitial connective tissue was so abundant in some of the ganglions that I could not avoid

the conclusion that hyperplasia of this tissue had taken place. Wandering cells also were present in greater abundance throughout the interstitial tissue in some of the ganglions in my series than was indicated by the account of Craig and Kernohan. In the ganglions of four patients in the series, as already stated, these cells were particularly abundant around small blood vessels. Like some of the earlier investigators, particularly Stämmler (1923), I regarded these phenomena as indicative of chronic inflammation of the ganglions in which they were present.

Some of my preparations also exhibited more extensive destruction of ganglion cells in the presence of free cells within the ganglion cell capsules than is indicated by the account of Craig and Kernohan. Although they observed indentations in ganglion cells in the presence of free cells within the capsules, they did not regard this as indicative of phagocytosis, since débris having an affinity for silver could not be demonstrated in the intracapsular cells. In view of the extensive destruction of ganglion cells, in the presence of free intracapsular elements, which I observed in some of my preparations, I assumed that some at least of the free cells within the ganglion cell capsules were phagocytes. This also was in agreement with the interpretation of Spiegel and Adolf[6] (1922), who reported extensive destruction of sympathetic ganglion cells by the phagocytic action of free cells within the ganglion cell capsules. According to their observations, neuronophagia may be brought about both by phagocytes which invade the ganglion cell capsules and by cells derived from the endothelium lining the capsules.

The functional significance of the changes in the sympathetic ganglions and ganglion cells described is as yet not fully known. That changes in the volume ratios of the nucleus and the cytoplasm of nerve cells and changes in the quantity of chromidial substance in their cytoplasm are correlated with cell activity, however, has been demonstrated experimentally. In an extensive study of the cytologic changes brought about in the Purkinje cells in the cerebellum, in experimental animals subjected to continued stimulation, Dolley[7] (1911) described an orderly sequence of change involving the nucleus-plasma ratio and the chromidial substance. The initial response of these cells to stimulation, according to Dolley, was an increase in size and increased production of chromidial substance, so that the cells became hyperchromatic. Following this phase, the cells began to shrink and the hyperchromatism receded, but the nuclei showed evidence of edema, and the nucleus-plasma ratio was shifted in favor of the nucleus. As the chromidial

6. Spiegel, E. A., and Adolf, M.: Die Ganglien des Grenzstranges, Arb. a. d. neurol. Inst. a. d. Wien Univ. **23**:67, 1922.

7. Dolley, D. H.: Studies on the Recuperation of Nerve Cells After Functional Activity from Youth to Senility, J. M. Research **24**:309, 1911.

substance was diminished beyond the normal level for the resting cell, secondary restoration of this substance set in. At first it was piled up about the nuclear membrane and then displaced toward the periphery. Following this phase, diminution of the chromidial substance again set in and continued until little chromidial substance or none remained apparent in the cytoplasm. The nucleus also appeared to be almost entirely devoid of chromatin. During this phase, the nucleus shrank, and the nucleus-plasma ratio was shifted in favor of the cytoplasm.

Studies of the effects of stimulation on the autonomic ganglion cells comparable to those of Dolley on the effects of stimulation of the Purkinje cells were not available. Some significant data bearing on the effects of stimulation on the ganglion cells of the celiac plexus, however, were at hand. A sequence of change in the chromidial substance and the nucleus-plasma ratio in these cells in the albino rat, which, in the main, paralleled that described by Dolley in the Purkinje cells, particularly in the dog, was described by Bradshaw [8] (1930) following exposure of the animals to roentgen rays and by Ingersoll [9] (1934) following stimulation of the abdominal viscera.

On the basis of studies of preparations of the celiac ganglions of normal rats at rest, both Bradshaw and Ingersoll classified the ganglion cells in three groups according to the quantity and distribution of the chromidial substance in the cytoplasm and the nucleus-plasma ratio. The cells of group I possess an abundant supply of chromidial substance which is distributed more or less uniformly throughout the cytoplasm. The great majority of the ganglion cells in the preparations of the ganglions of normal rats fall into this group. The cells of group II are, on the average, somewhat smaller than those of group I and possess less chromidial substance, which usually is distributed mainly in the perinuclear or the peripheral zone. Only a small percentage of the ganglion cells fall into this group. The cells of group III are, on the average, somewhat smaller than those of group II and possess still less chromidial substance. Some are almost devoid of this substance and exhibit only a little chromatin in the nucleus. This group is represented by only a few cells in the ganglions of the normal resting animals. By differential counting of the cells in the several groups in preparations of the celiac ganglions from normal resting animals and from animals which had been subjected to the means of stimulation already named, both Bradshaw and Ingersoll were able to demonstrate a progressive decrease in the percentage of the ganglion cells in group I and an increase in the percentage of those in groups II and III as the duration or the intensity of the stimulation was increased.

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8. Bradshaw, V.: Unpublished thesis, 1930.

9. Ingersoll, E. H.: The Effect of Stimulation upon the Coeliac Ganglion Cells of the Albino Rat, J. Comp. Neurol. **59**:267 (April) 1934.

According to Ingersoll, the initial response of the celiac ganglion cells to stimulation seems to be the increased production of chromidial substance, which results in hyperchromatism and slight enlargement of the cells. After this, the chromidial substance is diminished until it approaches the normal level and the cell undergoes some reduction in size, with a shifting of the nucleus-plasma ratio in favor of the nucleus. If stimulation is continued, the chromidial substance undergoes further diminution until the cytoplasm is practically devoid of this substance. Having given up most of its chromatin, the nucleus also appears pale and vesicular. These observations support the assumption that chromidial substance is produced and consumed during the activity of the ganglion cells. During the early phases of activity, its production exceeds its consumption and the result is hyperchromatism. During the later phases, chromidial substance is consumed more rapidly than it is produced and its supply gradually becomes depleted.

In view of these experimental data, which indicate that prolonged ganglion cell activity results in diminution in the amount of chromidial substance in these cells, the assumption seems to be warranted that the meager supply of chromidial substance present in the majority of the ganglion cells in most of the preparations in my series indicated overstimulation. In most of the patients in question, hyperactivity of the sympathetic ganglion cells also was indicated by the secretory activity of the sweat glands of the cold extremities and the hypertonus of the musculature of the peripheral blood vessels which, before operation, resulted in diminution of the blood supply to the extremities.

In some of the cases in the series the abundant infiltration of the interstitial tissue in the ganglions with wandering cells, probably lymphocytes and mononuclear leukocytes, strongly suggested the existence of a chronic inflammatory process in the ganglions, which might be regarded as a stimulating factor. On the other hand, in diseases such as chronic polyarthritis, it is unnecessary to assume that the hyperactivity of the sympathetic ganglion cells is due to stimulation which arises within the ganglions. The sweat secretory activity and the vasoconstriction in the extremities could be accounted for on the basis of reflex responses through the sympathetic nerves to stimulation of sensory end-organs in the vicinity of the inflamed joints. The afferent impulses in question reach the spinal cord via somatic afferent fibers where they activate preganglionic neurons through the usual somatovisceral reflex connections. The vasoconstriction in the extremity brought about in this manner in turn doubtless aggravates the inflammatory processes in the vicinity of the joints. It also is conceivable that the peripheral sweat secretory and vasoconstrictor neurons may become hyperactive by reason of medulliadrenal hyperactivity, hyperirritability of the visceral centers

in the central nervous system or inflammation of the sympathetic ganglions resulting from intoxications or infectious processes not primarily associated with the joints.

Patients with certain vasomotor neuroses, e. g., Raynaud's disease, exhibit a more or less constant hypertonus of the arteries, particularly the arterioles of the extremities, in the absence of apparent peripheral inflammation, and this is aggravated by subjection of the extremities to low external temperature. In cases of this sort the hypertonus of the peripheral arteries indicates hyperactivity of the sympathetic neurons supplying the extremities or of the corresponding visceral centers in the central nervous system. The vasoconstrictor hyperactivity, regardless of whether it is a causative factor in the disease process in question or merely an accompaniment of the disease, may play an important rôle in the course and sequelae of the disease, particularly by reason of its effect on the blood pressure and the distribution of the blood volume in the body.

As previously stated, many of the ganglion cells in nearly all of the ganglions in the series under discussion contain melanotic pigment. According to Dolley [10] (1917) and Dolley and Guthrie [11] (1918), in experimental animals the accumulation of pigment in nerve cells is always associated with chronic functional depression. These investigators were unable to produce pigmentation in nerve cells by stimulation ranging from normal activity to functional senility. The accumulation of pigment in the autonomic ganglion cells in man doubtless can be explained most satisfactorily on the assumption that it is associated with functional depression of the ganglion cells. In spite of this assumption, however, the presence of pigment in many of the ganglion cells in most of the ganglions in the present series is not incompatible with the theory that other changes in the ganglions are associated with hyperactivity of the ganglion cells. Melanotic pigment is a highly stable substance, which, having been deposited in ganglion cells, may remain there indefinitely. A moderate amount of pigment in ganglion cells therefore need not be regarded as indicative of the functional state of the cells. It probably indicates only a previous state of functional depression. In general, it may be stated that the accumulation of pigment in the autonomic ganglion cells increases with advancing age. In rare instances, however, heavily pigmented ganglion cells have been observed in young individuals. Ganglion cells heavily laden with pigment are probably

10. Dolley, D. H.: The Recovery from Depression in the Purkinje Cells and the Decline of Senility of Depression; with the Incidental Histogenesis of Abnormal Pigmentation, J. Comp. Neurol. **28**:465, 1917.

11. Dolley, D. H., and Guthrie, F. V.: The Pigmentation of Nerve Cells, J. M. Research **34**:123, 1918.

always deficient in chromidial substance. Some of these doubtless represent cells which are no longer functional.

The shrunken hyperchromatic ganglion cells present in my preparations conformed very closely in cytologic structure to Dolley's [12] (1913) description of hyperchromatic neurons in the central nervous system, particularly Purkinje cells in the cerebellum, in a state of physiologic depression. The lighter staining ganglion cells in my preparations which exhibited hyaline changes in the cytoplasm also conformed more or less closely, in cytologic structure, to Dolley's description of physiologically depressed hypochromatic Purkinje cells. According to Dolley's observations physiologic depression of the nerve cells results in cessation of the production of chromidial substance in the cytoplasm, accumulation of chromatin in the nucleus and a shift in the nucleus-plasma ratio in favor of the nucleus. If the neuron contains an abundance or an excess of chromidial substance when depression sets in, discrete chromidial granules become less and less apparent, and the acid-staining elements of the cytoplasm become more and more evident. The chromidial substance in the cytoplasm gradually is consumed, and that which remains becomes finely granular or goes into solution. In erythrosin-toluidine-blue preparations, the cytoplasm assumes a diffuse blue or reddish color, depending on the degree of change, and, particularly in the later phases of depression, a hyaline appearance. If the neuron contains only a meager supply of chromidial substance when physiologic depression sets in, the cytoplasm may assume a hyaline appearance without the intense staining reaction.

In view of the cytologic resemblance of the shrunken hyperchromatic ganglion cells and many of the lighter-staining ganglion cells showing evidence of hyalinization of the cytoplasm in my preparations to neurons of experimental animals known to be in a state of physiologic depression, it seems not improbable that the changes referred to in these cells were indicative of physiologic depression. As previously stated, ganglion cells exhibiting these changes were present in only small numbers in most of my preparations, whereas the majority of ganglion cells present afforded evidence of overstimulation. Shrunken hyperchromatic ganglion cells also may be observed in preparations of the sympathetic ganglions of normal animals (cats). The presence of physiologically depressed ganglion cells in small numbers in the sympathetic ganglions should therefore probably not be regarded as indicative of the functional state of the sympathetic nerves.

Certain substances, e. g., toxins, which in dilute solutions stimulate ganglion cells, in less dilute solutions depress these cells. It is therefore

12. Dolley, D. H.: The Morphology of Functional Depression in Nerve Cells and Its Significance for the Normal and Abnormal Physiology of the Cell, J. M. Research **29**:65, 1913.

not inconceivable that some ganglion cells, under appropriate conditions, may be depressed by the agents responsible for the stimulation of the majority of the ganglion cells in the same ganglions.

The existence in relatively large numbers of ganglion cells which exhibited evidence of physiologic depression in the preparations of the ganglions of certain patients in the present series strongly suggested that physiologic depression of sympathetic ganglion cells was related to the diseases in question, in these cases, or to other pathologic processes present. It was doubtless significant that of the patients with Raynaud's disease and chronic polyarthritis, i. e., diseases with which peripheral vascular hypertonus and other manifestations of sympathetic hyperactivity, e.g., hyperhidrosis, are known to be associated, the preparations of the ganglions of only one exhibited ganglion cells showing evidence of physiologic depression in large numbers. The case record of this patient also afforded evidence of toxicity. The existence of melanotic pigment in many of the ganglion cells and the presence of numerous ganglion cells showing other evidences of physiologic depression in the ganglions of the patient, who was 11 years of age and who had progressive muscular dystrophy, strongly suggested, in the absence of a record of other significant pathologic conditions, that physiologic depression of sympathetic ganglion cells, in this case, was related to the disease in question. The existence of numerous ganglion cells showing evidence of physiologic depression in the ganglions of the patient with paralysis agitans does not warrant the conclusion that physiologic depression of sympathetic neurons is related to this disease, since this patient gave a history of inflammatory rheumatism and sleeping sickness. The patient with endarteritis, preparations of whose ganglions exhibited many ganglion cells showing evidence of physiologic depression, as previously stated, also gave a history of alcoholism and addiction to drugs. The assumption that physiologic depression of the sympathetic neurons was related to the endarteritis, in this case, therefore, is unwarranted. Regardless of the possible relationship of physiologic depression of sympathetic ganglion cells to the disease process in certain cases in the present series, the total histopathologic picture of the ganglions could not be regarded as specific for the disease in question in any of these cases.

It seems not improbable that some of the swollen ganglion cells as well as those which underwent advanced neuronophagia in the present series of preparations had ceased to be functional. These, however, constituted only a small percentage of the total number of ganglion cells, the loss of which probably was functionally insignificant.

As stated in the preceding section of this paper, the histopathologic changes observed in the preparations of the sympathetic ganglions in this surgical series belong to the same general categories and cannot be

regarded as specific for the disease in question in any case. The case records of most of the patients in our series also indicated the existence of pathologic conditions not directly related to the disease in question, either preceding the latter or coincident with it. The changes observed in the preparations of the ganglions, therefore, at least in some of the cases, doubtless were associated with other pathologic conditions, as well as with the disease for which sympathectomy was carried out. As the histopathologic changes observed in most of the sympathetic ganglions in our series are indicative of hyperactivity of the ganglion cells, however, it seems not improbable that these changes and the associated autonomic dysfunction played a rôle in the disease processes in question, at least in those cases in which vasoconstriction was a factor in the disease. Possibly, physiologic depression of sympathetic ganglion cells, in those cases in which it is evident in a large percentage of the ganglion cells, also played a rôle in the disease process in question.

SUMMARY

All of the preparations of cervical and lumbar sympathetic ganglions removed surgically from thirty patients exhibited histologic changes which probably deviated from the range of normal variations. These changes included infiltration of the interstitial tissue with wandering cells, mainly lymphocytes and mononuclear leukocytes, the presence of free cells within the capsules of many of the ganglion cells, neuronophagia of some of the ganglion cells, diminution of the chromidial substance in the cytoplasm of a large percentage of the ganglion cells, deposition of melanotic pigment in a variable percentage, marked edema of a small number and, in some cases, hyaline degeneration and vacuolation of ganglion cells.

The presence of wandering cells in large numbers in the interstitial tissue in some cases was regarded as evidence of chronic inflammation in the ganglions, which probably affected the functional state of the ganglion cells. The diminution of the chromidial substance in the ganglion cells probably was associated with hyperactivity of these cells. The presence of a moderate amount of pigment in ganglion cells was not regarded as indicative of the functional state of the cells; it probably indicated a previous state of physiologic depression. Marked shrinkage of hyperchromatic ganglion cells, disintegration of the chromidial bodies and hyaline changes in the cytoplasm were regarded as indicative of physiologic depression of the cells.

The changes observed in the ganglions in individual cases were not specific and could not be related directly to the disease in question. The functional states of the ganglion cells with which these changes were associated, however, probably played a rôle in the disease process.

LOCAL ATROPHY OF BONE

I. EFFECT OF IMMOBILIZATION AND OF OPERATIVE PROCEDURES

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Fractures and operative procedures which are followed by prolonged immobilization of an extremity lead to a variable degree of atrophy of the bones of the extremity. This atrophy may be an important factor in the prolonged disability which often follows such injuries or operations. The observations recorded in this paper were made in an effort to determine whether or not atrophy of the bones will occur if a normal extremity is immobilized and whether the atrophy which follows fractures and operations is due to the immobilization or is due to the injury and changes in the circulation incident to the healing of the injury.

The various types of general and local atrophy and resorption of the bones have been considered elsewhere.[1] For the maintenance of normal structure of the bones it is necessary that an animal consume and utilize an adequate diet and that the bone be subjected to normal use. Deficient diet or abnormal metabolism leads to general atrophy of the bones, and disuse leads to local atrophy.

In spite of the general acceptance of the term "atrophy of disuse" as applied to bone, the knowledge of the occurrence of atrophy in normal extremities which have been immobilized rests on very few observations. This subject was studied in laboratory animals by Grey and Carr [2] and by Allison and Brooks.[3] In most of their experiments the disuse was

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1. Key, J. A.: Bone Atrophy and Absorption, Internat. J. Orthodont. **15**:949, 1929; Factors in Atrophy of Bone, J. Am. Dent. A. **17**:1660, 1930. Key, J. A.; Elzinga, E., and Fischer, F.: Local Atrophy of Bone: II. Effect of Local Heat, Massage and Therapeutic Exercise, Arch. Surg., to be published.

2. Grey and Carr: An Experimental Study of the Factors Responsible for Noninfectious Bone Atrophy, Bull. Johns Hopkins Hosp. **26**:381, 1915.

3. Allison and Brooks: Bone Atrophy, an Experimental and Clinical Study of Changes in Bone Which Result from Nonuse, Surg., Gynec. & Obst. **33**:250, 1921.

obtained by sectioning the nerves to the extremity. In the light of theories that atrophy of the bones is caused by increased circulation (Pommer [4] and Leriche and Policard [5]) a limb which has been paralyzed by section of the nerves cannot be considered normal. However, Grey and Carr immobilized one extremity of each of two rabbits in a plaster of paris cast, and Allison and Brooks immobilized one extremity of each of four dogs in a plaster of paris cast. In each instance the bones of the immobilized extremity became atrophic. The observers concluded that the changes which occurred in the bone were practically the same as those which occurred in the paralyzed limbs, and that it made no difference whether the disuse was caused by plaster casts or by section of the motor nerves to the part.

The lack of definite observations on the occurrence of atrophy of the bones in normal extremities is perhaps one reason why the atrophy which occurs after fractures and operations on the extremities is often ascribed to the injury or operation rather than to the lack of use. The same is true of the atrophy which occurs in limbs in which tuberculosis or some other chronic disease exists. Is the atrophy of the bones due to the disease itself, to hyperemia induced by the disease or to lack of use?

EXPERIMENTAL WORK

In an attempt to answer the question as to whether or not immobilization in a plaster cast will cause atrophy of the bones in a normal extremity in a human being, we selected ten patients who were in the hospital for some condition of the upper extremities and who had normal lower extremities. With the patients' consent we applied comfortable plaster of paris casts to both lower extremities. The casts were bivalved and were strapped on. As we were using these patients to determine the effects of various forms of physical therapy on atrophy of the bone, the casts were removed twice a day while one limb was subjected to baking or massage or exercise. The routine was continued for from four to six weeks.

The presence of and the degree of atrophy were determined by studying roentgenograms of the feet. Lateral roentgenograms of each foot were made at the beginning of the experiment and again at the end of the period of immobilization. In order that the roentgenograms might give a true picture of the changes which occurred in the bones the length of the exposure, the position of the foot and the distance of the tube were kept as uniform as possible. The uniformity of the roentgenograms was further controlled by noting the density of the shadow cast by the soft tissues. We assumed that the density of the soft tissues did not change perceptibly during the period of immobilization, and we discarded those roentgenograms in which the shadows of the soft tissues were not approximately the same as those in the controls of the same foot taken before the period of immobilization.

Comparison of the roentgenograms showed that at the end of six weeks definite atrophy of the bones had occurred in the normal feet which had been immobilized.

4. Pommer, G.: Origin and Diagnostic Significance of Osteoporosis, Arch. f. klin. Chir. **136**:1, 1925.

5. Leriche, R., and Policard, A.: Physiology of Bone, translated by Moore, Sherwood, and Key, J. A., St. Louis, C. V. Mosby Company, 1928, p. 81.

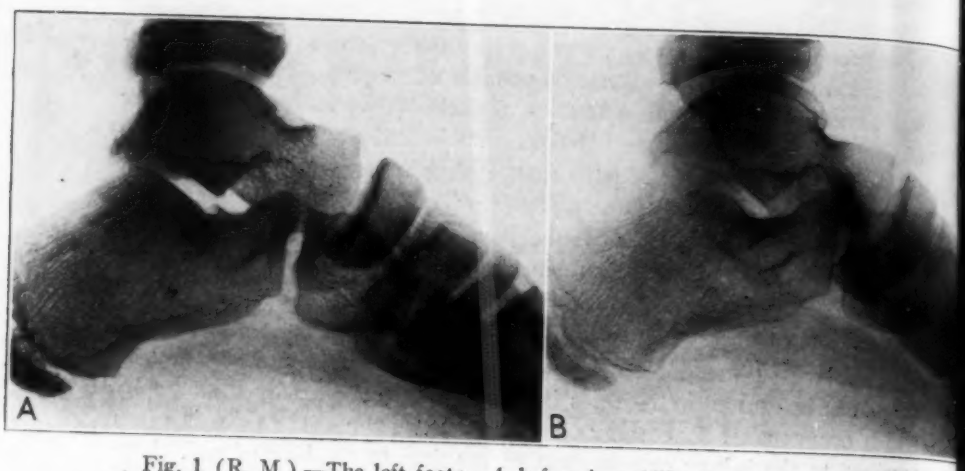

Fig. 1 (R. M.).—The left foot: *A*, before immobilization, and, *B*, after eight weeks of immobilization in a plaster of paris cast.

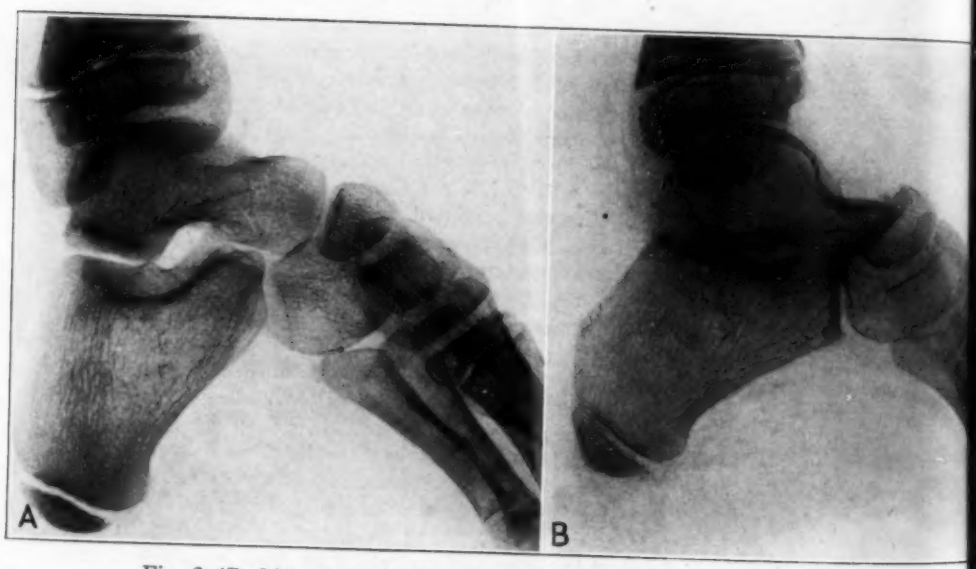

Fig. 2 (R. M.).—The right foot: *A*, before immobilization, and, *B*, after the Hoke operation and eight weeks of immobilization in a plaster of paris cast. The control foot is shown in figure 1.

This atrophy was evidenced by a diffuse rarefaction of all the bones of the foot and the lower ends of the tibia and fibula which were included in the roentgenograms. As a result of the rarefaction the shadows cast by the bones were less dense and the trabeculae stood out more clearly in the roentgenograms made at the end of the period of immobilization. This change was most clearly visible in the os calcis, astragalus, scaphoid and cuboid bones.

Having determined that atrophy of the bones does occur in normal extremities which are immobilized, and having obtained a fair idea of the amount of change to be expected, we selected forty patients who were to be subjected to various types of operation on the lower extremities and obtained lateral roentgenograms of the feet before operation and at periods of from four to twelve weeks after operation. In several instances in which one foot was normal, we examined this foot roentgenologically before the operation, immobilized it in a plaster cast and studied it again by roentgen ray at the end of the period of observation. Thus we had a normal control on the same person. In other instances we used as controls the normal feet referred to in the preceding paragraph.

The majority of the patients had stabilizing operations on the feet, but osteotomies for the correction of deformities, manipulations for clubfoot, arthrodeses of the hip or knee and operations on the soft tissues were included in the series.

Studies of the roentgenograms of the extremities operated on revealed definite atrophy in the bones of the feet. This could be detected in the roentgenograms taken four weeks after operation, but was more marked in those taken after ten or twelve weeks. In the postoperative roentgenograms of feet which had been immobilized for twelve weeks the trabeculae were smaller in diameter and less numerous than in the preoperative roentgenograms of the same feet. It thus appears that many trabeculae may be resorbed within the short space of three months. However, comparison of the roentgenograms of the feet of the extremities on which operation had been done with those of normal extremities which had been immobilized in plaster of paris casts over the same period of time led to the conclusion that there was approximately the same amount of atrophy in each. In other words, the atrophy of the bones was caused by the immobilization, and the operations on the bones or soft tissues of the extremity did not appreciably alter the rate or degree of the atrophy.

There was one exception. This occurred in a boy who had an osteotomy at the knee for the correction of a flexion deformity which had been caused by septic arthritis. Pyogenic infection appeared in the wound after the operation and an abscess and considerable fever developed. In this case the atrophy of the bones in the left foot (on which the operation was done) was definitely more pronounced than it was in the right (normal) foot. This one case indicates that the presence of an acute pyogenic infection may accelerate the resorption of the bones in that extremity as compared with that which occurs in the normal extremity which is immobilized but is not infected.

In several of the extremities on which an operation was done a variable amount of atrophy was present in the bones of the foot before the operation. In these the final roentgenograms showed an increase in the atrophy. The increase was proportional to the period of immobilization, and appeared to be independent of the state of the bone when the immobilization was started. Thus, atrophy of disuse is a progressive phenomenon, and when an extremity in which the bones are atrophic is immobilized there is a further resorption of the bones of this extremity.

In addition to the observation of atrophy of the bones in older children, we studied roentgenograms of the feet of younger children taken before and after immobilization, and found that the immobilization with or without surgical inter-

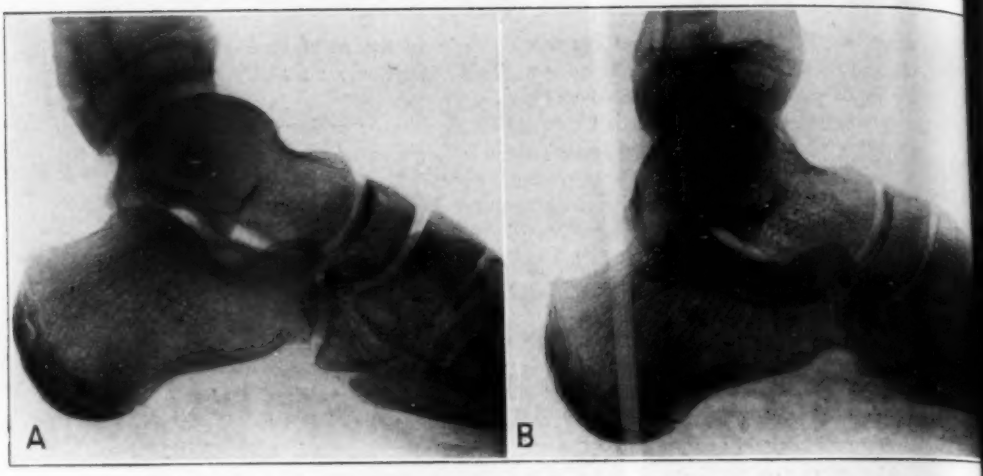

Fig. 3 (L. C.).—The right foot: *A*, before immobilization, and, *B*, after ten weeks of immobilization in a plaster of paris cast.

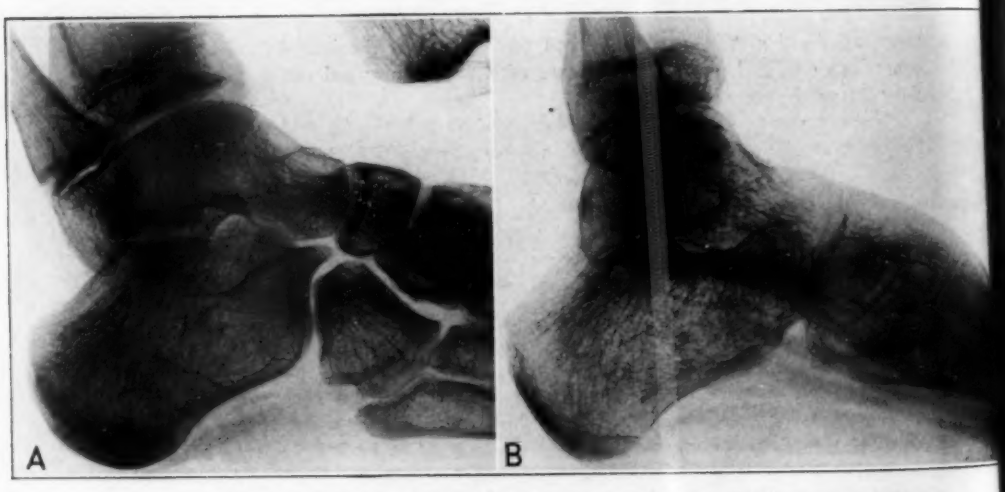

Fig. 4 (L. C.).—The left foot: *A*, before operation, and, *B*, after an osteotomy at the knee and ten weeks of immobilization in a plaster of paris cast. The operative wound became infected. The bone atrophy is more pronounced in this foot than in the control foot shown in figure 3.

vention or manipulation of the foot caused atrophy of the bones just as it did in older children. We were interested to note, however, that the later roentgenograms of the feet of the younger children showed a definite increase in the size of some of the centers of ossification in the bones of the tarsus, and in some instances new centers of ossification appeared. It is thus evident that formation of new bone may proceed in an extremity simultaneously with progressive resorption. In the older children, as a rule, no difference could be detected in the size of the bones, but in certain instances the apophysis of the os calcis was definitely larger in the later roentgenograms with atrophy than it was in the preoperative roentgenograms before the atrophy began. We have made no observations on the rate of growth of bone during the period of immobilization, but the clinical observation that the bones of a limb which had been subjected to a long period of disuse during the period of growth are apt to be shorter and smaller than those in the opposite limb indicates that lack of use tends to decrease the rate of growth in the bones of an extremity, but does not completely arrest growth.

COMMENT

It may be objected that the immobilization of a limb in a plaster of paris cast has a definite effect on the circulation in the extremity and that any change which occurs in the limb cannot be attributed merely to the lack of use, but is more likely the result of a change in the circulation of the part. It is true that the circulation in a limb which is immobilized in a plaster cast is not normal. But we have no reason to believe that the circulatory change is due to the cast. It is probably due to the lack of use of the muscles of the part and to the lack of normal strain of bearing weight. Furthermore, there is no evidence to indicate that this change in the circulation is the cause of the atrophy of the bones. If the atrophy were due to circulatory changes the atrophy would be more marked in extremities which have been subjected to accidental or to operative trauma, with resultant marked changes in the circulation. Since we have shown that practically the same degree of atrophy occurs in the bones of extremities in which surgical intervention has occurred as in normal extremities which are immobilized, we believe that the atrophy exhibited in our cases was due to the lack of use and that it was not due to any increase or decrease of the circulation.

However, we do not ignore or attempt to explain the acute atrophy of the bones which may occur after an injury. This acute traumatic atrophy of Sudeck has not been produced experimentally and its mechanism is unknown. It may be due to local circulatory changes which are more marked than those which occur after an operation, but it is more reasonable to believe that the acute atrophy of the bones which occasionally follows an injury and which usually occurs in the vicinity of an infection is due to some chemical alteration in the fluids of the tissues in the involved area.

CONCLUSIONS

1. Immobilization of an extremity leads to atrophy of the bones of this extremity.

2. This atrophy can be detected in roentgenograms taken four weeks after the immobilization began.

3. The atrophy is progressive, and if an extremity with atrophic bones is immobilized, further atrophy of these bones may be expected.

4. Operative or accidental trauma does not appreciably increase the atrophy incident to the immobilization.

5. The presence of a pyogenic infection in the extremity appears to increase the local atrophy of the bones.

6. The growth and formation of new bone may occur simultaneously with local atrophy of a given bone.

LOCAL ATROPHY OF BONE

II. EFFECT OF LOCAL HEAT, MASSAGE AND THERAPEUTIC EXERCISE

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DETROIT

During the past fifteen years physical therapy has assumed an important place in the armamentarium of physicians, and large amounts of time and money are expended in administering various forms of physical therapy to patients who are ill or who are convalescing from disease or from accidental or operative injuries. Naturally a considerable literature has accumulated on the subject, but the observations are largely clinical and are not carefully controlled. Consequently, the beneficial effects claimed for various physical therapeutic procedures cannot be accepted without reservations, because due allowance must be made for the enthusiasm of the physician and for the desire of the patient to get well, while little credit is given to the natural tendency of the injured tissues to heal and resume their normal functions.

As a matter of fact, a large percentage of the physical therapy which is used today is prescribed and administered empirically. This is particularly true of the baking, massage and exercises which are regarded by many as the sine qua non for the efficient care of patients who have suffered injuries of the bones or joints or who have been subjected to orthopedic operations. This empiricism is due to the lack of carefully controlled experimental work, and the lack of experimental work is due to the fact that administration of physical therapy to laboratory animals is laborious and estimation of the results is difficult, while the opportunity for making adequately controlled observations on patients does not often present itself.

The extensive studies of Hartman, Blatz and Kilborn [1] are a notable exception. These observers showed that massage and active contractions

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1. Hartman, F. A.; Blatz, W. E., and Kilborn, L. G.: Studies in the Regeneration of Denervated Mammalian Muscle: II. Effect of Massage, J. Physiol. **53**: 108, 1919; III. Effects of Massage and Electrical Treatment, ibid. **53**:290, 1919; IV. Effects of Massage and Electrical Treatment in Secondary Sutures, ibid. **54**:392, 1920.

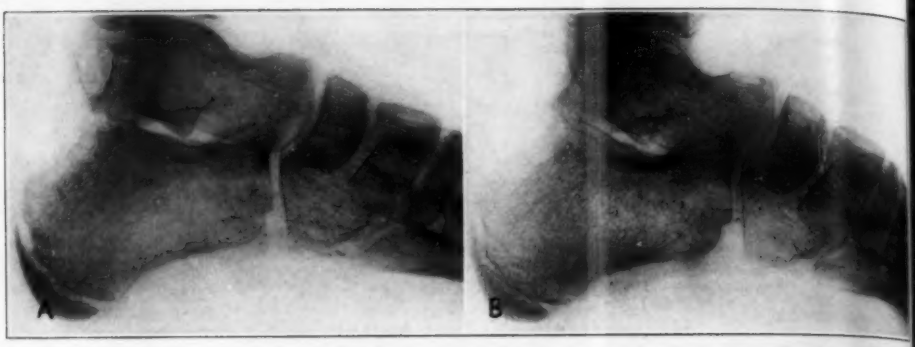

Fig. 1 (P. T.).—The left foot: *A*, before immobilization, and, *B*, after six weeks of immobilization in a plaster of paris cast.

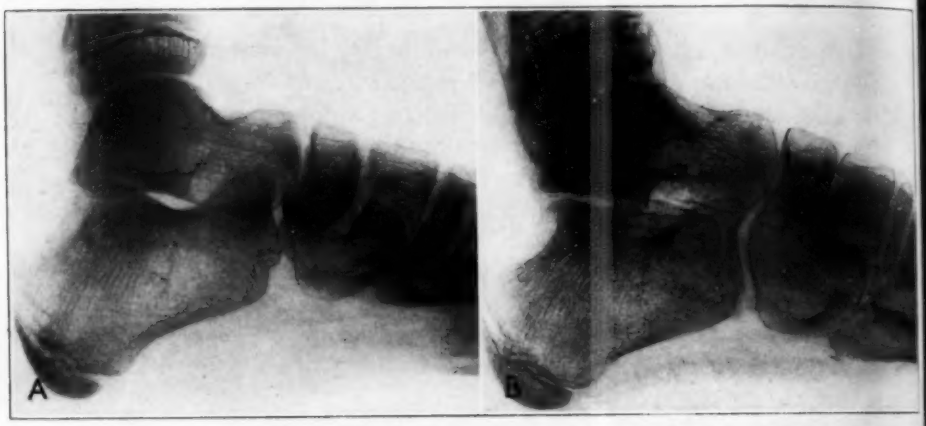

Fig. 2 (P. T.).—The right foot: *A*, before immobilization, and *B*, after six weeks of immobilization in a plaster of paris cast. The foot and leg were massaged twice a day during the period of immobilization. The control is shown in figure 1.

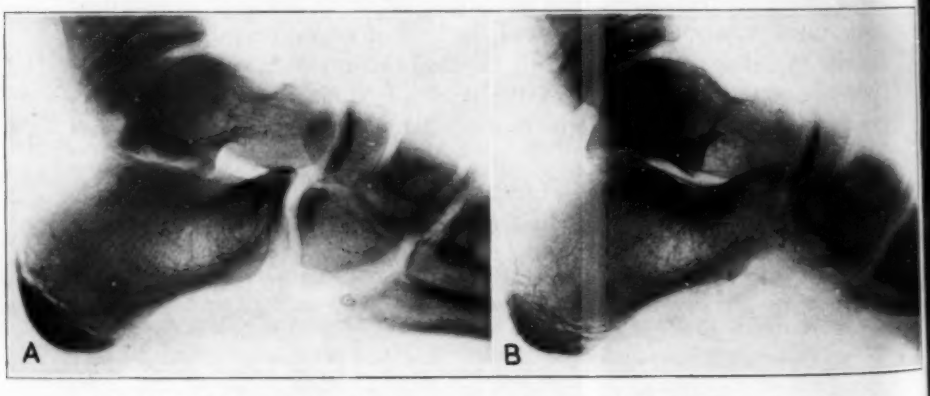

Fig. 3 (J. D.).—The right foot: *A*, before immobilization, and, *B*, after six weeks of immobilization in a plaster of paris cast. This foot and leg were baked twice a day during the period of immobilization.

of the muscles induced by a slow surging galvanic current had no beneficial effect on the soleus, gastrocnemius and plantaris muscles of rabbits which had been paralyzed by cutting the sciatic nerves.

We shall attempt to evaluate the effects of heat, massage and therapeutic exercise on bones in which local atrophy was being induced by

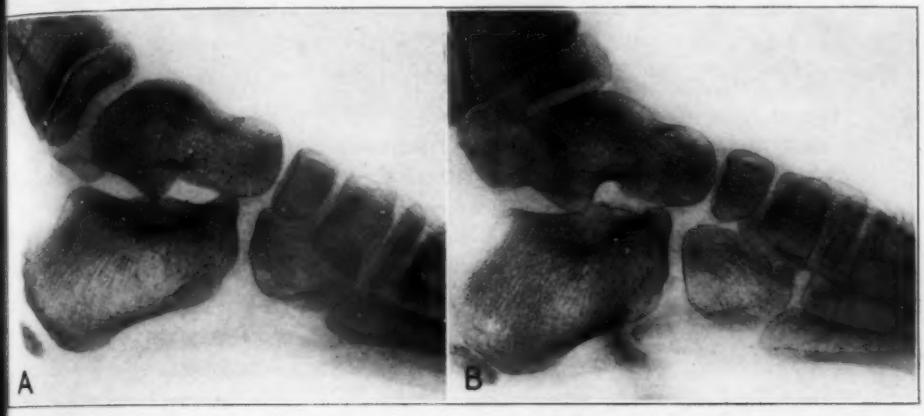

Fig. 4 (A. R.).—The left foot: *A*, before immobilization, and *B*, after six weeks of immobilization in a plaster of paris cast.

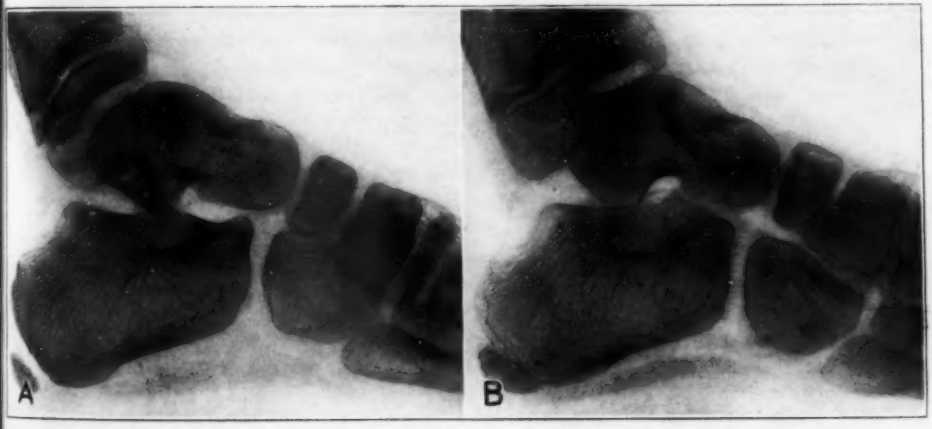

Fig. 5 (A. R).—The right foot: *A*, before immobilization, and, *B*, after six weeks of immobilization in a plaster of paris cast. This foot was exercised twice a day during the period of immobilization. The control is shown in figure 4.

disuse, and in a later paper we hope to evaluate the effects of the same procedures on normal muscles which are being rendered atrophic by disuse. Having established the facts that if the normal lower extremity of a child from 10 to 12 years of age is immobilized in a plaster of Paris

cast for a period of from four to twelve weeks, the bones of the immobilized foot will become atrophic, and that this atrophy will progress at such a rate that it can be detected in roentgenograms of the foot taken four weeks after the beginning of the immobilization, we were in a position to study the effect of massage, local heat and therapeutic exercise on bone. Consequently, the following experiment was undertaken:

EXPERIMENTAL WORK

Ten patients with normal lower extremities and no general disease were selected. These were patients of suitable age who were willing to cooperate in the experiment and who were in the hospital for the treatment of some deformity or paralytic condition of one or both upper extremities. The experiment did not prolong their stay in the hospital or work any undue hardship on them.

Each lower extremity, with the foot at a right angle to the leg and the knee slightly flexed, was encased in a comfortable plaster of paris cast which extended from the toes to the upper third of the thigh. After the plaster had hardened the casts were bivalved and strapped on. The left lower extremity was used as the control and the right lower extremity was subjected to baking, massage or exercise. In five of the ten patients, the right lower extremity was baked, in two massaged and in three exercised.

In order to make the control as exact as possible the cast was removed from the left lower extremity while the physical therapy was being given to the right lower extremity. The experiments lasted for six weeks, and the physical therapy was given twice a day. Uniform roentgenograms of both feet in two planes were taken at the beginning and at the end of the experiment.

The degree of atrophy of the bones which occurred was estimated by comparing the roentgenograms taken before and after the period of six weeks. It was found that the lateral view of the foot and ankle was most satisfactory and that the astragalus, os calcis, scaphoid and cuboid were the bones which showed the most constant changes. Decrease in the density of the bones as a whole, decrease in the size and number of the trabeculae and decrease in the thickness of the cortex were considered evidence of atrophy. The relatively slight degree of atrophy which was produced by immobilization for six weeks was characterized by decrease in the density of the bones as a whole; the changes in the size and number of the trabeculae were relatively slight, while no changes could be detected in the thickness of the cortex. The decrease in the density of the bones caused the trabeculae to stand out more clearly in the atrophic bones.

At the end of the experiment the children were permitted to resume their normal activities. The movement in the joints and power in the muscles were soon restored without specific treatment, and the patients suffered no ill effects from the period of immobilization.

RESULTS

Local Heat.—The local heat was applied in the form of dry (radiant) heat supplied by an ordinary electric baker with carbon light bulbs. The right foot and lower part of the leg were placed in the baker for twenty minutes twice a day. Comparison of roentgenograms taken at the end of the period with those taken before the experiment began

showed that definite atrophy of the bones occurred in all of the feet which were immobilized and that the atrophy was of practically the same degree in the bones of the control limbs as in those which were baked.

Massage.—The massage was administered to the right leg and foot by a trained physical therapist and was continued for ten minutes twice a day. Comparison of the roentgenograms taken before and at the end of the experiment showed that atrophy of the bones occurred in all of the immobilized feet and that this atrophy was of practically the same degree in the controls as in those which were massaged.

Exercise.—The exercises were as follows: "1. Raise the right leg as high as possible with the knee straight, and lower it. 2. Flex the right hip and knee as far as possible; then extend the leg on the thigh and lower the foot to the bed. 3. Dorsiflex the foot and curl the toes; then plantarflex the foot and curl the toes. Do each exercise slowly twenty-five times, twice a day." The physical therapeutist was responsible for the execution of the exercises as prescribed. Comparison of the roentgenograms taken before and at the end of the experiment showed that atrophy of the bones occurred in all of the immobilized feet, and the degree of atrophy was practically the same in the bones of the control limbs as in those which were exercised.

COMMENT

The observations recorded in this paper are not presented as evidence that it is not possible to affect atrophy of the bones by physical therapy, but are presented as evidence that baking, massage and exercise in the amounts in which these measures are used clinically have no appreciable effect on the local atrophy of the bones which is caused by immobilization of the part.

It is probable that no amount of massage or passive movement which could be tolerated by the patient would have any appreciable effect on the atrophy. However, if the voluntary muscular exercises were carried out more frequently it would be possible to lessen or to prevent atrophy of the bones, in which case there would be little immobilization or disuse. In regard to local heat, we believe that this tends to accelerate the atrophy incident to disuse. We have seen patients with local atrophy of the bones which we believe was partly caused by the enthusiastic and prolonged use of baking or of diathermy.

CONCLUSION

Short periods of local heat, massage or active exercise have little, if any, effect on local atrophy of the bones which occurs when an extremity is immobilized in a plaster of paris cast.

DISTENTION OF THE URINARY BLADDER

I. HEMATURIA AND SUDDEN EMPTYING; AN EXPERIMENTAL AND CLINICAL STUDY

C. D. CREEVY, M.D.
MINNEAPOLIS

Sudden emptying of the chronically distended urinary bladder, especially in prostatic hypertrophy, has been condemned as hazardous for so long that the idea has become a tradition. The Ebers papyrus gives a prescription to prevent the too rapid escape of urine.[1] The conception that one must withdraw the urine slowly first received wide recognition early in the nineteenth century. It was then gradually lost to view, only to reappear with the comparatively recent development of prostatic surgery.

I recently reviewed the literature dealing with the reaction to rapid decompression of the distended bladder; at this time only the portion which refers to the relationship of rapid decompression and bleeding will be reviewed in detail. The most widely accepted explanation of the supposed danger of rapid emptying of the bladder in cases of chronic retention maintains that the intravesical pressure is elevated as a result of the retention. This elevated tension is alleged to be transmitted to the kidneys. The blood vessels of the urinary tract are said to adapt themselves to the heightened pressure, so that the sudden withdrawal of the urine leads to prompt dilation of the vessels with rupture and hemorrhage into the tissues and lumens of the urinary tract. The congestion and hemorrhages thus produced are assumed to interfere with the renal function to the point of causing uremia and even death.

While this makes an admirable theory, it is by no means so free from objection as one might be led to believe from a casual survey of the literature. It is only recently that its soundness has been questioned. Prätorius[2] said not long ago that he had never seen a case of this

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Abridgment of part of a thesis submitted to the faculty of the graduate school of the University of Minnesota in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Surgery.

1. Garrison, F. H.: An Introduction to the History of Medicine, Philadelphia, W. B. Saunders Company, 1921.

2. Prätorius, G.: Ueber die erstmalige Behandlung hochgradiger Harnverhaltungen, Deutsche med. Wchnschr. **55**:875, 1929.

ex vacuo bleeding. Bazy [3] declared that the distended bladder should be emptied promptly and kept empty. Brecher and Chwalla,[4] after a study of three hundred cases, concluded that gradual withdrawal of the urine possesses no advantages over simple catheterization; the latter procedure does not appear to increase the incidence of hematuria or of untoward reactions of any kind. Rose [5] observed that he could see no objection to rapid withdrawal of the urine provided the bladder is kept empty thereafter. I [6] recently analyzed a series of seventy-one cases which came to autopsy after catheterization for urinary retention due to prostatic hypertrophy. I was forced to conclude that rapid emptying of the bladder is of itself harmless, and that gradual decompression, far from possessing advantages, may even be dangerous in that it prolongs the period of inadequate drainage with its attendant increased liability to infection. The following objections to the idea that the sudden relief of chronic or subacute retention is harmful were found:

1. Other sources of hematuria are available in prostatism; it has been shown both experimentally and clinically that these may, alone or in combination, cause the various phenomena seen after sudden relief from obstruction.

2. No incontrovertible proof exists that sudden emptying of the bladder can of itself produce bleeding or other untoward reactions.

3. Death following catheterization is due almost invariably to an infectious process, either renal (80 per cent) or extrarenal (20 per cent).

4. Hematuria may fail to follow catheterization in circumstances which would certainly produce it if it were due to mechanical factors.

5. Bleeding accompanies gradual as well as sudden evacuation of the urine.

6. That a constant elevation of the intravesical tension exists in obstruction remains to be shown. That is, it is not certain that spontaneous decompression does not occur.

7. Gradual, as compared to sudden, decompression has not lowered the mortality of patients catheterized for retention of the urine from prostatic enlargement. Two series of cases, alike except for the rate of emptying of the bladder, were compared; they showed no difference in the mortality following treatment.

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3. Bazy, P.: Note sur la pathogénie, le diagnostic, et le traitement des pyélonéphrites suppurées, Bull. et mêm. Soc. d. chirurgiens de Paris **22**:263, 1896.

4. Brecher, E., and Chwalla, R.: Neues zur Behandlung der Harnretention nebst Untersuchungen über die Entlastungsreaktion, Ztschr. f. urol. Chir. **31**:266, 1931.

5. Rose, D. K.: Clinical Application of Bladder Physiology, J. Urol. **26**:91, 1931.

6. Creevy, C. D.: The Effect of Sudden Emptying of the Chronically Distended Bladder, Arch. Surg. **25**:356, 1932.

CAUSE OF THE HEMATURIA

Leaving aside the propriety of sudden, as compared with gradual, emptying of the chronically distended bladder, it is interesting to inquire as to the possible cause of the bleeding which so often follows the catheterization of patients with chronic partial urinary retention.

The literature names four possible causes other than complications like neoplasm and urolithiasis, namely, urinary retention, sudden emptying of the bladder, infection and trauma.

Retention of Urine.—This can of itself cause hematuria; the presence of vascular congestion and engorgement in the prostate, bladder, ureters and kidneys of patients with obstruction at the vesical outlet has been known for years and commented on by many observers, among them Mercier [7] (1861), Grellety,[8] Picard,[9] Tuffier,[10] Genouville and Boeckel,[11] Delbet,[12] Chute [13] and Vintici and Laroche [14] 1929). They attribute the congestion to venous stasis resulting from an increase in the intravesical tension. Its existence is verified clinically by the frequent occurrence of bleeding following even the gentlest urethral manipulation in patients with prostatic obstruction.

This stasis in prostatic retention may produce hemorrhage into the urinary tract, since Bernard,[15] Albarran,[16] Sedillot,[17] Escat,[18] Walker,[19]

7. Mercier, A.: Note sur l'hématurie qui suit le cathétérisme dans quelques cas de rétention d'urine, Union méd. de Paris **9**:41, 1861.

8. Grellety, M.: Mécanisme des accidents mortels qui dans certains cas accompagnent l'évacuation trop prompte de la vessie, France méd. **25**:146, 1879.

9. Picard, M.: Les dangers du cathétérisme chez les vieillards, France méd. **26**:106, 1879.

10. Tuffier, T.: Rôle de la congestion dans les maladies des voies urinaires, Thèse de Paris, 1885, p. 149.

11. Genouville, M., and Boeckel, A.: Physiologie pathologique du cathétérisme, in Pousson, A., and Desnos, E.: Encyclopedie française d'urologie, Paris, Gaston Doin & Cie, 1914, vol. 4, p. 944.

12. Delbet, P.: Rétention et incontinence d'urine, in Pousson, A., and Desnos, E.: Encyclopédie française d'urologie, Paris, Gaston Doin & Cie, 1914, vol. 6, p. 492.

13. Chute, A. L.: Observations on Cases of Prostatic Obstruction Presenting Overdistended Bladders, Boston M. & S. J. **167**:607, 1912.

14. Vintici, V., and Laroche, A.: Hemorrhagies de la prostate, J. d'urol. **28**: 140, 1929.

15. Bernard, M. C.: A Simple Method of Relieving Retention of the Urine in Diseases of the Prostate Gland, Dublin M. J. **17**:369, 1847.

16. Albarran, J.: Etude sur le rein des urinaires, Thèse de Paris, Paris, Jouve & Cie, 1889.

17. Sedillot, C.: Des accidents graves qui suivent parfois le cathétérisme et les autres opérations pratiquées sur l'urétère, Gaz. d. hôp. **4**:546, 1861.

18. Escat, J.: Des hématuries rénales chez les prostatiques, Thèse de Paris, 1897, p. 1.

19. Walker, K. M.: The Risks of Prostatectomy, Practitioner **112**:278, 1924.

Young [20] (3.6 per cent of nine hundred and eighty-three cases or 14.1 per cent of those with large amounts of residual urine), Bumpus and Foulds [21] (5 per cent of eighty-three patients with distended bladders) and Vintici and Laroche [14] encountered bleeding in apparently uncomplicated prostatic hypertrophy.

Further proof that urinary retention may cause hematuria is found in the literature on experiments. Guyon and Albarran [22] and, later, Shigematsu [23] ligated the urethra in dogs and rabbits, thereby producing hemorrhages at first in the vesical submucosa, later in the detrusor urinae and finally in the renal parenchyma.

Other evidence is found in the fact that ligature of the ureter also causes bleeding. Fabian [24] (guinea-pig), Corbett [25] (dog) and Helmholz and Field [26] (rabbit) observed bleeding into the renal parenchyma and into the wall and lumen of the pelvis within eighteen hours of experimental ureteral occlusion.

Sudden Emptying of the Retained Urine.—This has always been regarded as productive of hematuria, but the actual importance of this factor is difficult to evaluate. Desormeaux [27] drew an analogy between postcatheterization and postpartum bleeding, although, since the retained urine is not attached by a placenta the separation of which leaves a raw surface, this analogy is impossible. Le Grand,[28] Guyon [29] and Blum and Rubritius [30] spoke of hemorrhage *ex vacuo,* but failed to explain how a vacuum may develop in a collapsible organ with flexible

20. Young, H. H.: Hydraulic Pressure in Genitourinary Practice, Especially in Contracture of the Bladder, Bull. Johns Hopkins Hosp. **9**:100, 1898; Practice of Urology, Philadelphia, W. B. Saunders Company, 1926, vol. 1, p. 17.

21. Bumpus, H. C., Jr., and Foulds, G. S.: Gradual Emptying of the Overdistended Bladder, J. A. M. A. **81**:821 (Sept. 8) 1923.

22. Guyon, J. F., and Albarran, J.: Anatomie et physiologie pathologique de la rétention d'urine, Arch. de méd. expér. et d'anat. **2**:181, 1890.

23. Shigematsu, H.: Etude expérimentelle de la rétention d'urine, J. d'urol. **25**:16, 1928.

24. Fabian, E.: Die Niere des Kaninchens nach der Unterbindung ihres Harnleiters, Biblioth. med. Abt. Path. u. path. Anat. **18**:1, 1904.

25. Corbett, J. F.: Changes in the Kidney Resulting from Tying the Ureter, Am. J. M. Sc. **144**:568, 1912.

26. Helmholz, H. F., and Field, R. S.: Acute Changes in the Rabbit's Kidney, Particularly the Pelvis, Produced by Ligating the Ureter, J. Urol. **15**:409, 1926.

27. Desormeaux, M.: Hemorrhagie vésicale mortelle à la suite du cathétérisme, Bull. et mêm. Soc. d. chirurgiens de Paris **50**:743, 1851.

28. Le Grand, A.: Union méd. de Paris, 1860, p. 471; quoted by Mercier.[7]

29. Guyon, J. F.: Rétention d'urine: Forme aiguë et forme chronique, Gaz. d. hôp. **52**:481, 1879.

30. Blum, V., and Rubritius, H.: Klinik der Prostatahypertrophie, in von Lichtenberg, A.; Voelcker, F., and Wildbolz, H.: Handbuch der Urologie, Berlin, Julius Springer, 1926, vol. 5, p. 585.

walls. Countless writers have attributed vesical and renal hemorrhage (Young [20] has seen bloody urine issuing from the ureters after catheterization of the distended bladder) to the emptying alone, but have failed to consider the objections just named.

Other potent objections exist. First, gradual emptying of the bladder does not protect against bleeding. Van Zwalenburg's [31] patient bled; so did 5 per cent of the eighty-three patients of Bumpus and Foulds,[21] as well as 48.7 per cent of the patients in thirty-three fatal cases which I reported.

Moreover, the relief of enormous vesical distentions may fail to cause hemorrhage. Lund, Corner [32] and Bury [33] each reported a case of chronic, partial retention due to incarceration of a retroflexed gravid uterus; they withdrew 13,960, 4,000 and 4,900 cc. of urine, respectively, without causing bleeding. Pinkham [34] and Hamman [35] reported the removal of 7,900 and 7,000 cc. from elderly patients with prostatism without bleeding.

If postcatheterization bleeding is actually due to mechanical factors (a fall of tension with bursting of the vessel walls), these discrepancies are difficult to explain. If, on the other hand, it is due to other factors, such as trauma or infection, the explanation is easy. The wide variations in the amount of trauma from catheterization are too obvious to require comment; variations in the virulence of bacteria and in the susceptibility of the hosts are part of everyday knowledge.

Rôle of Infection.—The rôle of infection in the production of hematuria has been underestimated.

Goodhart [36] was apparently one of the first to realize that urinary retention predisposes to infection (1873). He found renal abscesses at autopsy in 20 per cent of a large series of patients with obstruction of the neck of the bladder and the urethra. This clinical observation was soon supported experimentally by Albarran,[16] Rovsing,[37] Melchior [38] and

31. Van Zwalenburg, C.: Emptying a Chronically Distended Bladder; Description of a Simple Device, J. A. M. A. **75**:1711 (Dec. 18) 1920.

32. Corner, M. C.: An Interesting Case of Retention to the Amount of a Gallon, Lancet **2**:130, 1905.

33. Bury, B. W.: A Case of Retention of Urine, Brit. M. J. **1**:936, 1911.

34. Pinkham, J. G.: Distention of the Bladder Mistaken for Ascites, M. Rec. **10**:1065, 1875.

35. Hamman, D. J. H.: Extreme Bladder Overdistention, Brit. M. J. **1**:141, 1906.

36. Goodhart, J. F.: On Erysipelas of the Kidney and Urinary Tract, Guy's Hosp. Reports **19**:357, 1873-1874.

37. Rovsing, P.: Pathogenese und Behandlung der septischen Infektion der Harnwege, Monatsbl. d. Krankh. d. Harn.-u. Sex.-Appar. **3**:506, 1898.

38. Melchior, M.: Berichte über 52 bakteriologisch untersuchte Fälle von infectiösen Erkrankungen der Harntracte, Monatsbl. d. Krankh. d. Harn.- u. Sex.-Appar. **3**:584, 1898.

others. Rovsing and Melchior also called attention to the fact that trauma, like retention, increases the liability of the urinary tract to bacterial invasion.

Infection, either alone or in combination with retention, can cause severe bleeding. Albarran [16] pointed out that often the only demonstrable lesion in early acute pyelonephritis consists of leukocytic infiltration and of hyperemia or hemorrhage. Escat [18] reported the finding of a hydronephrosis filled with blood, in which the cause of the bleeding was a bacterial inflammation. Koch,[39] using the staphylococcus, and Sweet and Stewart,[40] using Bacillus coli, produced hemorrhages into the renal parenchyma in association with a suppurative nephritis following the intravenous injection of these organisms. The frequency of severe hematuria during acute glomerulonephritis, which is bacterial in origin, is familiar to every physician.

Hemorrhage coincident with the onset of infection in the course of prostatic obstruction has been reported by Escat,[18] Chute,[13] Hyman, Elfving [41] and me.[6]

Instrumental Trauma.—Trauma caused by instruments also may lead to bleeding in the patient with prostatic obstruction. Indeed, it was at first blamed for the fatal reactions following catheterization (Finlayson [42] and Tuffier [10]); Escat [18] said that he had never seen hematuria follow an easy, gentle catheterization. While trauma undoubtedly plays a part in the production of postcatheterization bleeding, it can scarcely be regarded as the sole cause, particularly since patients who die of such reactions usually, if not invariably, exhibit renal lesions, and since Young [20] saw blood issue from the ureters of patients who were bleeding after catheterization. As only a small percentage of patients with uncomplicated prostatic obstruction bleed spontaneously, other explanations have been sought.

EXPERIMENTAL AND CLINICAL STUDY

In order to present a fairly complete chain of evidence as to the origin of postcatheterization bleeding in urinary retention, five series of experiments were performed. Series 1 consisted of twelve dogs in

39. Koch, J.: Ueber die Hämatogene Entstehung der eitrigen Nephritis durch den Staphylokokkus, Ztschr. f. Hyg. u. Infektionskr. **61**:301, 1908.

40. Sweet, J. E., and Stewart, L. F.: Ascending Infections of the Kidney, Surg., Gynec. & Obst. **8**:460, 1914.

41. Elfving, A. K.: Ueber Blutdruck und Nierenfunktion der Prostatiker, Acta Soc. med. fenn. duodecim **9**:1, 1928.

42. Finlayson, J.: Case of Extensive Submucous Ecchymosis in the Bladder and Hemorrhage into the Tubules of the Kidney, Occurring Within Two Days from a Single Catheterization, Glasgow M. J. **21**:132, 1884.

which simple acute retention of the urine was established, the animals being killed and examined at intervals thereafter.

In series 2 comprising eight animals, the conditions of the first group of experiments were duplicated, except that after an interval the retention was relieved. The animals were killed later.

Series 3 consisted of two dogs in which a chronic partial urinary retention was established by incomplete urethral ligature. In both animals hematuria developed; they were included to demonstrate the relationship of hematuria to infection engrafted on obstruction. This series was reenforced by the inclusion of a number of clinical cases.

Series 4 comprised six dogs, in which the procedure mentioned in connection with the first group was carried out, but in addition the spinal cord was sectioned in the middorsal region in order to observe the effect of distention of the bladder without voluntary attempts to urinate.

In series 5 the bladders of four animals were distended rapidly with comparatively high pressures under anesthesia, while the abdomen was open. In four more animals, stretching of the vesical wall was prevented by enclosing the bladder in a rigid bag.

Series 1: Simple Acute Retention as a Cause of Hematuria.—Twelve normal male dogs, varying in weight from 12 to 16 Kg., were used. After tests had shown that the urine and the nonprotein nitrogen of the blood were normal, the animals were anesthetized by the subcutaneous injection of morphine sulphate supplemented by the local injection of 0.5 per cent procaine hydrochloride. Under sterile conditions, the penis was then isolated in the perineum behind the bone, its vessels were stripped off and preserved, and the urethra was occluded by a ligature of linen tape. The animals were then allowed to recover in metabolism cages. Only those that passed no urine while the ligature was in place were included in this study. They were allowed to eat and drink at will. This series of experiments was divided into three groups.

The first group consisted of three dogs killed with chloroform twenty-four hours after occlusion of the urethra; the second group comprised six dogs killed after forty-eight hours, and the third, three dogs killed after from sixty to seventy-two hours.

After the retention had lasted for the required period, the animals were anesthetized with chloroform, the abdomen opened and the bladder inspected. A sterile large-caliber needle was inserted into the bladder through the anterior wall, and the intravesical pressure was recorded by means of a vertical glass tube. Urine was then aspirated for culture, measurement and urinalysis. The anesthesia was then deepened until death occurred; autopsy was performed.

Certain animals died; similar observations were made except that the pressure and the ability of the bladder to contract during emptying could not be observed.

EXPERIMENT 1.—In a male dog weighing 18 Kg., with a twenty-four hour acute retention, the nonprotein nitrogen one hour before death was 17 mg. for each 100 cc. of blood. The bladder held 625 cc. of sterile urine which contained a few red blood cells; the intravesical tension was 4 cm. of water, and the viscus contracted on being emptied. At autopsy the thoracic and abdominal cavities showed nothing abnormal except the distended bladder. Histologically, the kidneys and ureters were normal. There were a few small hemorrhages beneath the vesical mucosa, which was intact (fig. 1).

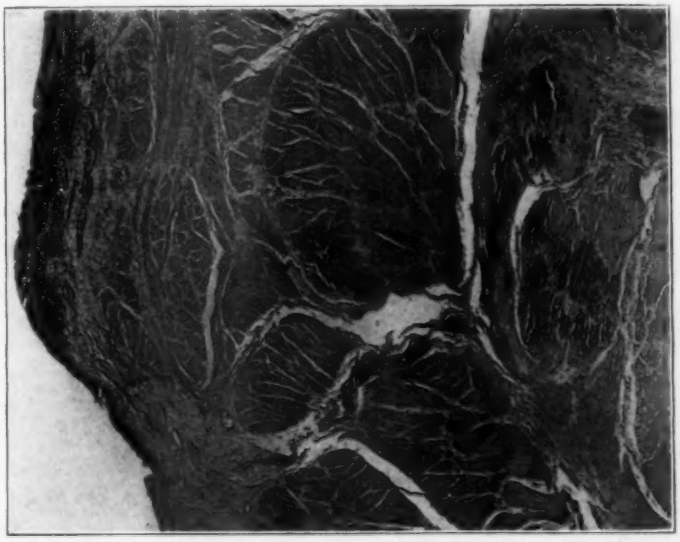

Fig. 1 (experiment 1).—Early hemorrhage into the wall of the bladder resulting from obstruction for twenty-four hours.

EXPERIMENT 2.—In a male dog weighing 12 Kg., with a twenty-four hour obstruction, the antemortem nonprotein nitrogen was 20 mg. per hundred cubic centimeters. The bladder was cyanotic and contained 560 cc. of sterile urine, in which several red blood cells were found in each high power field. The pressure was 18 cm. of water. When the bladder was emptied, its color returned to normal. Autopsy revealed nothing unusual. Microscopic examination of the kidneys, ureters and bladder revealed nothing abnormal.

EXPERIMENT 3.—A male dog weighing 15 Kg., with a twenty-four hour retention, was given 1,000 cc. of a physiologic solution of sodium chloride subcutaneously following urethral ligature; the dose was repeated on the following morning. The nonprotein nitrogen was 25 mg. before death. The bladder contained 805 cc. of faintly turbid, sterile urine with many red blood cells and a few white cells in each high power field. The bladder was plum-colored and markedly distended; the tension was 21 cm. of water. The discoloration disappeared as the bladder

contracted on being emptied. On section, one saw in the kidneys a mild engorgement of the vessels of the medulla which could not be regarded as abnormal. The ureters showed no changes. Beneath the vesical mucosa, particularly in the posterior midline, were several hemorrhages varying from 0.5 to 3 mm. in diameter, and a few submucous petechiae scattered over the base and dome (fig. 1).

Comment.—In three normal male dogs, ligation of the urethra for twenty-four hours produced no definite renal lesions except in one animal (experiment 3); here the picture was that of engorgement of the capillaries and of the veins which was not sufficiently marked to justify conclusions. The bladder was regularly the seat of a few small hemorrhages beneath the mucosa, particularly in the midline of the posterior wall. The distended bladder appeared cyanotic, but returned to its normal color on being emptied. The nonprotein nitrogen of the blood did not rise, nor were abnormally formed elements other than a few red cells found in the urine.

These results are in contrast to those of Guyon and Albarran [22] and of Shigematsu,[23] who regularly found small hemorrhages in the kidney and a rise in the nonprotein nitrogen of the blood (the blood in the urea was found by Guyon and Albarran; the rise in the nonprotein nitrogen, by Shigematsu) twenty-four hours after obstruction of the urethra. However, these findings were to be anticipated for several reasons:

1. The urinary output of dogs given a constant intake of fluid is extremely irregular. At the outset of these experiments it was intended to make estimations of the renal function by determination of the chemical constituents of the urine before, during and after retention without catheterization. It was found that, in a series of ten dogs given a constant intake of 500 cc. every twenty-four hours and a weighed diet of ground beef the daily output of urine varied from 50 to 1,200 cc., while the chemical constituents of the urine varied within equally wide limits. These discrepancies are evidently due to the male dog's habit of emptying the bladder incompletely.

2. On several occasions, during abdominal operations on dogs of average size with undisturbed urinary tracts, I have seen bladders holding as much as 1,300 cc. in the absence of evidence of obstruction.

3. Dogs kept in cages void less often than those allowed to run about, evidently in anticipation of freedom. It may be that the dogs studied by Guyon and Albarran were not caged and therefore tried to void more often than the animals which were caged.

It was therefore expected that a twenty-four hour obstruction would not produce lesions unless, as in experiment 3, fluids were forced.

Because definite damage did not appear in this group of animals, the second group of six dogs with obstruction of approximately forty-eight hours' duration was studied.

EXPERIMENT 4.—A dog weighing 20 Kg. died forty-eight hours after ligature of the urethra. The nonprotein nitrogen of the blood was 125 mg. three hours before death. Autopsy revealed the presence of bronchopneumonia. The kidneys and ureters were engorged. The bladder was plum-colored and distended with 800 cc. of sterile urine containing many white cells. When the bladder was emptied post mortem, the color of its external surface returned practically to normal, but the wall remained flaccid and wrinkled. There were, however, numerous elevated hemorraghic areas with raised margins, particularly on the posterior wall, on the mucosal aspect.

On microscopic examination, the kidneys showed patchy areas in which the epithelium of the convoluted tubules and of Henle's loop were swollen and vacuolated, partially occluding the lumens, which in many areas contained hyaline and granular casts. These areas were most numerous immediately beneath the renal

Fig. 2 (experiment 6).—Kidney following retention for forty-eight hours.

capsule. The vessels about the collecting tubules were choked with blood, and there were a few small hemorrhages beneath the pelvic mucosa, which was intact. The ureters were normal.

The bladder showed many large hemorrhages beneath the mucous membrane. The mucosa was missing over many of these areas, and a few of the hemorrhages extended into the muscular coat for a short distance.

EXPERIMENT 5.—In a male dog weighing 20 Kg. the nonprotein nitrogen was 80 mg. after a forty-eight hour retention. The dog was anesthetized. The bladder held 1,300 cc. of sterile urine containing a few red and white blood cells. The external surface of the bladder was plum-colored, but it became practically normal when the bladder was emptied. Contraction was incomplete. At autopsy, in addition to the presence of lesions like those seen in experiment 4, there were a few small cortical hemorrhages which adjoined the swollen tubules. The ureters were normal, while the bladder showed the changes seen in the preceding experiment.

EXPERIMENT 6.—In a male dog weighing 26 Kg. death occurred forty-eight hours after ligation of the urethra. The nonprotein nitrogen two hours before death was 60 mg. per hundred cubic centimeters. At autopsy the kidneys were a dark bluish-red, and the capsular vessels were prominent. On section there were hemorrhagic streaks radiating from the pelvis and ending a short distance beneath the capsule. The peripelvic fat was edematous. The bladder was plum-colored, but the external surface cleared on the withdrawal of 600 cc. of sterile urine containing albumin, a few white cells, numerous red cells and many triple phosphate crystals. The bladder wall remained somewhat flaccid after the withdrawal of the urine. On microscopic examination (fig. 2), there were large, linear, radially arranged hemorrhages extending from the pelvis to the capsule and often joining one another beneath the capsule; the pelvic mucosa was elevated and the peri-

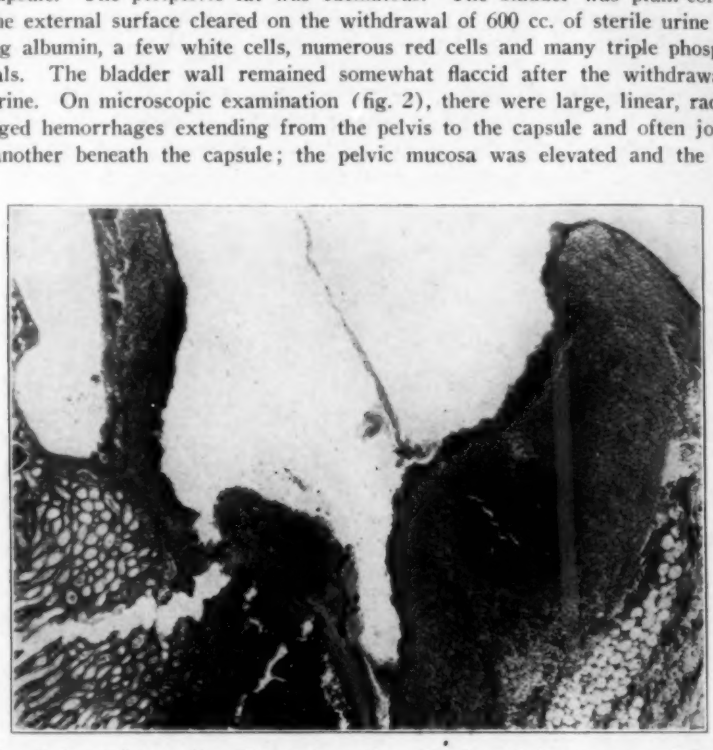

Fig. 3 (experiment 6).—Hemorrhage beneath the pelvic mucosa and into the peripelvic fat.

pelvic fat invaded (fig. 3); the tubules adjoining the hemorrhages in the medulla and cortex stained poorly, and the nuclei were pyknotic or absent. The lumens of the tubules were partially or completely occluded and contained granular débris (fig. 4). Many glomeruli were choked with blood, but their capsules and epithelia appeared normal. The ureters showed a few small hemorrhages in the adventitia of the distal quarter. The bladder showed lesions similar to those in experiment 5, but in addition the hemorrhages had separated many muscle bundles. Those surrounded by extravasated blood were necrotic (fig. 5).

EXPERIMENT 7.—A dog weighing 25 Kg. was chloroformed forty-eight hours after urethral ligature. During the period of retention 5,500 cc. of water was given by stomach tube. The nonprotein nitrogen before death was 80 mg. The pressure of the bladder was 25 cm. The bladder was hugely distended and plum-colored, and on the posterior midline above the trigon was an elevated area of necrosis 6 cm. in diameter. The bladder held 1,800 cc. of sterile bloody urine

containing albumin and loaded with red blood cells. The discoloration persisted after the withdrawal of the urine, which left the bladder flaccid. The kidneys were similar to those in experiment 6. At autopsy the peritoneal cavity contained 100 cc. of clear fluid. There was definite edema of the retroperitoneal tissues, especially well marked in the perirenal fat. The ureters were definitely dilated in the distal quarter and appeared to be engorged with blood in this area. Microscopic examination revealed that the kidneys and ureters were like those in experiment 6. The necrosis of the bladder muscle was more widespread.

EXPERIMENT 8.—A dog weighing 26 Kg. died forty-eight hours after occlusion of the urethra. Autopsy revealed bronchopneumonia. The gross and microscopic observations were similar to those of experiments 6 and 7, except that the edema was less marked.

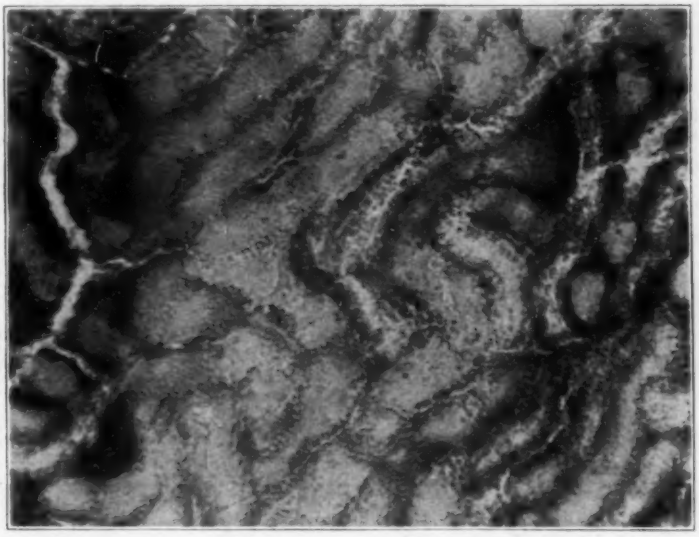

Fig. 4 (experiment 6).—High power magnification of an area of hemorrhage in the same kidney.

EXPERIMENT 9.—A male dog weighing 15 Kg. was killed with chloroform forty-eight hours after urethral ligature. The nonprotein nitrogen was 122.6 mg. before death. The bladder contained 1,200 cc. of sterile, bloody urine at a pressure of 36 cc.; it did not contract on being emptied. Except that the lungs were diseased, the observations at necropsy were similar to those of experiment 6, but the condition was even more advanced. The kidneys were hemorrhagic and softened, and the ureters definitely dilated, the dilation being confined to the lower one third of the kidney, which was hemorrhagic.

Comment.—The lesions produced within forty-eight hours were much more definite than those found after twenty-four hours. There is, however, considerable variation in the changes produced in different individuals by urinary retentions of the same duration. In experiments 4 and 5, for example, there were only moderate changes in the kidneys, while the bladder was more definitely damaged. In experiments 6 and

7, on the other hand, there was an advanced lesion in the kidneys characterized by radial linear hemorrhages passing through the medulla and the cortex and associated with marked necrosis in adjoining tubules, while the bladders were necrotic. It is also to be noted that in experiment 3 a retention of 800 cc. produced only a little damage within twenty-four hours, while a retention of 800 cc. in experiment 4 produced more marked changes in forty-eight hours, although dog 3 weighed only 15 Kg. and its bladder was therefore relatively less distended than that of dog 4, which weighed 20 Kg.

EXPERIMENT 10.—A male dog weighing 16 Kg. died seventy hours after urethral ligature. The nonprotein nitrogen forty-eight hours after ligature was 45 mg.; after seventy-two hours, 60 mg. Autopsy, which was performed immedi-

Fig. 5 (experiment 6).—Advanced hemorrhages into the wall of the bladder following retention for forty-eight hours.

ately after death, revealed purulent bronchopneumonia. The bladder was distended and plum-colored, and contained 300 cc. of turbid but sterile urine, with albumin, many red blood cells, a moderate number of white cells and many granular casts. There was no return to normal color, and the bladder did not contract after emptying. The kidneys were moderately softened and hemorrhagic. The ureters were normal. Microscopic examination revealed many small, peritubular hemorrhages in the cortex. Adjoining the hemorrhages were a few areas in which the tubules were swollen, with pale, vacuolated cytoplasm containing shrunken, deeply-staining nuclei. The bladder showed submucosal hemorrhages with invasion of the muscularis and mucosa, and necrosis.

EXPERIMENT 11.—A dog weighing 20 Kg. died seventy-four hours after urethral ligature. The bladder contained 1,000 cc. of sterile urine, in which innumerable red blood cells and a few white cells were found. The bladder was flaccid and blue-black; at the apex was a tear 3 cm. in diameter, from which the necrotic mucosa protruded. There was a tiny opening in the mucosa from which bloody urine escaped, thus explaining 800 cc. of bloody peritoneal fluid. The

peritoneum was everywhere intensely congested and exhibited small, fibrinous plaques. There were numerous hemorrhages in the free margin of the great omentum which was applied to the rent in the bladder. The kidneys showed lesions like those described in experiment 9. The lower one third of each ureter was moderately dilated. Microscopic examination of the kidneys revealed the typical radiating hemorrhagic streaks with necrosis of adjoining tubules and hemorrhages beneath the pelvic mucosa. The ureters contained small adventitial hemorrhages. The bladder exhibited numerous hemorrhages infiltrating the entire muscular wall, associated with sloughing of the overlying mucosa and necrosis of the invaded muscle.

EXPERIMENT 12.—A male dog weighing 28 Kg. was found dead sixty-eight hours after urethral ligature. The observations were similar to those in the preceding dog except that there was more advanced peritonitis, with 1,500 cc. of bloody urine in the abdominal cavity. The bladder was flaccid, gangrenous and empty, and there was a large perforation at the apex.

Comment.—Plainly the lesions of experimental acute retention are variable. After twenty-four hours the most prominent change observed was mild cyanosis of the vesical wall which disappeared on emptying of the bladder. A few small, submucous hemorrhages were seen, but the ureters and kidneys were normal. Within forty-eight hours the changes were intensified. The cyanosis was more striking, and large extravasations of blood invaded the bladder wall, especially posteriorly in the midline, where the blood supply was poor. Hemorrhagic lesions appeared also in the ureters and kidneys. In from sixty to seventy-two hours the bleeding into the bladder wall produced necrosis with rupture and urinary peritonitis. The rupture was always in the same situation. The lesions in the upper urinary tract were similarly more advanced.

Series 2: Rôle of Sudden Emptying of the Acutely Distended Bladder in the Production of Hematuria.—This series consisted of eight animals. The operative procedure was identical with that in the first series. After the obstruction was established, the animals were placed in metabolism cages and observed to make sure that no urine was passed. The obstruction was relieved after twenty-four, forty-eight and seventy-two hours by removal of the ligature. A catheter was passed, and the bladder pressure measured. All of the animals voided. Twenty-four hours later they were killed with chloroform and studied.

EXPERIMENTS 13 and 14.—In two animals weighing 18 and 19 Kg., respectively, the obstruction was relieved under local anesthesia after twenty-four hours. The bladder tensions were 17 and 23 cm., respectively. The urine which was voided at the time of the removal of the ligature contained a few red cells but was sterile. The urine which was subsequently passed was clear. The animals were killed twenty-four hours after ligature. No lesions were demonstrable at autopsy.

EXPERIMENT 15.—In an animal weighing 14 Kg. the obstruction was relieved without anesthesia after forty-eight hours. The pressure was 24 cm. The dog promptly voided 600 cc. of bloody, sterile urine. He was chloroformed twenty-four hours later. He had voided 1,000 cc. in the interval. The urine cleared grossly during this period; the last specimen voided before death contained a moderate

number of red blood cells. At autopsy the bladder held 50 cc. of smoky urine containing numerous red cells. In all other respects the observations at autopsy coincided with those in experiment 6.

EXPERIMENT 16.—In a male dog weighing 18 Kg. the tension was 30 cm. after a forty-eight hour retention. After removal of the ligature without anesthesia the animal voided 800 cc. of bloody sterile urine, and in the ensuing twenty-four hours 500 cc., the amount of blood in each successive specimen being less than that in the preceding one. At autopsy 25 cc. of smoky, sterile urine was observed. The bladder wall was hemorrhagic in the usual situation. There were mucosal petechiae. The kidneys were mildly engorged.

EXPERIMENT 17.—In a male dog weighing 14 Kg., after relief of a retention of seventy hours' duration, 200 cc. of bloody, sterile urine escaped under a pressure of 8 cm. of water, but the bladder was still palpable. Two hundred cubic centimeters of bloody urine was passed the ensuing day. The animal was anesthetized twenty-four hours after the removal of the ligature. The bladder wall was cyanotic and wrinkled and collapsed without contracting on the removal of 400 cc. of bloody urine. At autopsy the whole posterior wall was necrotic but intact. The ureters were dilated in their lower third, while the kidneys presented the picture seen in experiment 6.

EXPERIMENT 18.—In a male dog weighing 15 Kg., the obstruction was relieved sixty-eight hours afterward because the bladder was so distended that rupture was feared. Five hundred cubic centimeters of bloody urine at a pressure of 12 cm. was passed at once, leaving the bladder slightly distended. One thousand cubic centimeters was passed in the following twenty-four hours, with gradual clearing of the urine. At postmortem examination twenty-four hours after the relief of the retention, the bladder was contracted and hemorrhagic, and there was necrosis of the posterior wall. The ureters were slightly dilated at their lower ends; the kidneys were congested and showed radial streaks of hemorrhage.

Comment.—Sudden relief of acute urinary retentions of twenty-four, forty-eight, sixty-eight and seventy-two hours' duration did not produce results differing from those seen after simple retention. There was a marked tendency toward recovery, even within twenty-four hours, except in dog 17, in which the intramural hemorrhage was so advanced as to prevent muscular contraction. It seems evident, therefore, that at least in acute urinary retention the sudden relief of pressure is without undesirable effects. To test this observation further, experiments 19 and 20 were performed.

EXPERIMENT 19.—A dog weighing 21 Kg., immediately on the release of the ligature seventy hours after its application, voided 900 cc. of bloody urine under a pressure of 20 cm. The urine was sterile and contained red blood cells in gradually diminishing amounts for three days; it became normal on the fourth day, when the animal was killed. At autopsy the bladder contained 10 cc. of clear urine. The external surface was normal except posteriorly, where there was a hemorrhagic patch the size of a quarter. The ureters appeared normal, as did the kidneys.

Microscopically, the hemorrhagic area in the bladder wall was surrounded and invaded by leukocytes; the red cells had lost their outlines; a few fibroblasts were seen at the edges. The kidneys showed radially arranged streaks in which groups

of tubules were surrounded by leukocytes and young connective tissue; the epithelium of the tubules was basophilic and swollen and contained deep-staining nuclei.

EXPERIMENT 20.—In a male dog weighing 17 Kg. the obstruction was relieved seventy-two hours after ligation. The tension was 10 cm. Two hundred cubic centimeters of sterile bloody urine was evacuated at once; the bladder remained palpable. The dog voided 800 cc. during the ensuing twenty-four hours. At forty-eight hours the urine contained a few red blood cells. At seventy-two hours it was microscopically normal, and it remained normal until the animal was killed on the twenty-ninth day. Nothing abnormal was found at autopsy. Microscopic examination of the kidneys showed scattered radial streaks of connective tissue extending from the calices to the capsule and corresponding to the hemorrhagic bands seen in the early lesions. Adjoining the connective tissue an occasional tubule showed

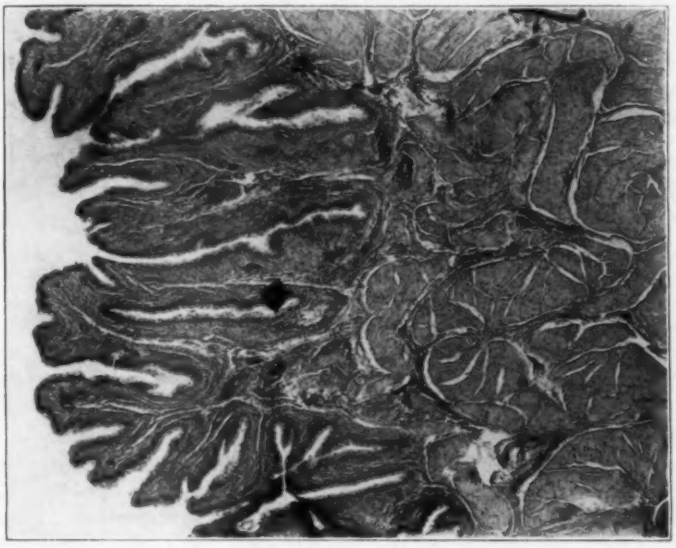

Fig. 6 (experiment 20).—Healing of the bladder twenty-nine days after severe damage. Only a few collections of lymphocytes show the site of the original lesion.

a few pale, faintly basophilic cells with flattened epithelium and deeply stained nuclei.

The bladder (fig. 6) showed only a few small collections of lymphocytes scattered through the interstitial tissue and penetrated, in a few areas, by young connective tissue cells.

Comment.—It is clear that sudden relief of an acute retention is harmless, since the animals recover.

Series 3: Relationship of Infection of the Urinary Tract to Hematuria.—In this series two experiments on dogs and two cases in man illustrated the relationship of hematuria to infection in the urinary tract.

EXPERIMENT 21.—A female dog weighing 28 Kg. showed normal urine. A valve was constructed of metal in such a manner as to allow fluid to pass through in a small stream. The valve was sterilized, inserted into the urethra and held in place by a tight ligature of linen tape surrounding the entire urethra. The dog voided slowly thereafter. Six weeks later urination was slow, difficult and frequent. Hematuria appeared and increased so rapidly in severity that within seven weeks after the operation the urine was extremely bloody. An enormously distended bladder was felt at this time.

The animal was killed with ether forty-five days after the operation. The bladder was distended and plum-colored. It contained 1,200 cc. of bloody urine. The mucosa was gangrenous. The metal valve had disappeared. Its former site was occupied by filiform stricture. The ureters and renal pelves were moderately dilated and edematous. The kidneys were increased in size. The parenchyma was softened and engorged. On section innumerable evenly distributed miliary abscesses were seen.

EXPERIMENT 22.—This experiment was identical with the foregoing except that the valve with the linen ligature around it was found in the bladder; the urethra contained a filiform stricture.

Comment.—The first two series showed clearly that acute urinary retention alone can produce hemorrhage into the urinary tract. The last two experiments prove that infection engrafted on chronic retention may produce or aggravate bleeding.

CASE 1.—A man, aged 72, said that he had had urinary difficulty of one year's duration. Prostatic hypertrophy was present. There was 20 cc. of sterile residual urine. Suprapubic cystostomy yielded a clear, sterile urine. The urine continued to be clear for seventy-two hours, when, coincident with a chill and a rise of temperature to 102 F., it became bloody. Culture then showed a streptococcic infection.

CASE 2.—A man, aged 72, had had difficult urination for several years. He had noticed a mass in the lower part of the abdomen three months before admission. Its appearance coincided with the onset of nocturnal incontinence. There was moderate diffuse enlargement of the prostate, and the bladder was palpable a fingerbreadth below the umbilicus.

Thirteen hundred cubic centimeters of clear, sterile urine was evacuated by suprapubic cystostomy. The urine remained clear for twenty-four hours, at which time the temperature rose to 100.4 F., and hematuria appeared. B. coli and streptococci were found on culture.

Comment.—In these cases there was hemorrhage from infection. In the first instance, there was only 20 cc. of residual urine. Seventy-two hours after the commencement of drainage, bleeding associated with bacteriuria appeared. Since decompression could not have occurred, the bleeding must be attributed to infection.

In the second case, the withdrawal of 1½ quarts (1.4 liters) of residual urine was followed by bleeding, but not until twenty-four hours afterward. How, except by an infectious process, can one account for the latent period?

The bleeding from trauma is too well known to require illustration, but a case illustrating the aggravation of bleeding by an acute pyelonephritis seems worthy of mention.

CASE 3.—A boy of 19 who had a contracted bladder secondary to a nontuberculous pyelonephritis of long standing bled during cystoscopy. Shortly thereafter he had a chill; the temperature rose to 103 F., and the bleeding increased. The blood urea rose to 90 mg., and the hemoglobin fell from 90 to 42, so that two days after the cystoscopy a transfusion was required.

Comment.—Hematuria in acute urinary retention may therefore originate from simple retention, from trauma or from infection (gangrenous cystitis or pyelonephritis). But what is the mechanism which produces the hemorrhage in simple retention? Is it a question of stretching of the bladder wall with, as has been suggested, tearing of the vessel walls, or is it a question of pressure? Series 4 and 5 were undertaken in an attempt to answer these questions.

Series 4-5: Origin of the Bleeding in Acute Urinary Retention.—The experiments in series 4 concerned the effect of stretching the bladder wall. Because of the varying effects of given retentions of similar duration it seemed probable that some factor other than contraction of the bladder wall must be concerned. It appeared not unlikely that this factor might be the attempts of the animal to empty the bladder. In order to test this theory, in six animals (experiments 23 to 28) the spinal cord was divided at the sixth dorsal segment in order both to prevent sensory impulses from the bladder from reaching the brain and to prevent straining (paralysis of the abdominal muscles). It was assumed that the well known reflex centers in the sacral cord (Budge,[43] Goltz,[44] Giannuzzi,[45] McClintic,[46] Mosso and Pellacani[47]) maintained the response of the bladder wall to distention in a fairly normal state.

EXPERIMENTS 23-24.—In two normal male dogs weighing 18 and 21 Kg. under ether anesthesia and with surgical asepsis, the sixth dorsal segment of the spinal cord was exposed and crushed with a ligature of linen tape surrounding the dura mater. Immediate paralysis of the hindquarters ensued. The urethra was ligated as described in connection with series 1. Forty-eight hours later the nonprotein nitrogen of the blood was normal. No leakage of urine had occurred. Under chloroform anesthesia the bladders were exposed. They were distended but

43. Budge, J.: Ueber das Centrum genitospinale des Nervus sympathicus, Virchows Arch. f. path. Anat. **15**:115, 1858; Zur Physiologie des Blasenschliessmuskels, Arch. f. d. ges. Physiol. **6**:306, 1872.

44. Goltz, F.: Ueber die Funktionen des Lendenmarks des Hundes, Arch. f. d. ges. Physiol. **8**:460, 1874.

45. Giannuzzi: Recherches physiologiques sur les nerfs moteurs de la vessie, J. physiol. de l'homme **6**:22, 1863.

46. McClintic, C. F.: The Clinical Neurophysiology of the Automatic Urinary Bladder and Enureses, J. Urol. **20**:267, 1928.

47. Mosso, A., and Pellacani, P.: Sur les fonctions de la vessie, Arch. ital. de biol. **1**:97 and 291, 1882.

of normal appearance, and contained 800 and 950 cc., respectively, of sterile, normal urine under pressures of 12 and 16 cm. The animals were killed. Autopsy showed nothing further. Microscopic examination of the kidneys, ureters and bladder showed no lesions.

EXPERIMENTS 25-26.— In two normal male dogs of 14 and 17 Kg. the same operative procedures as in experiments 23 and 24 were carried out. Seventy-two hours later the nonprotein nitrogen was normal. The bladders contained 1,100 and 1,550 cc., respectively, at tensions of 16 and 24 cm. of water. There was no discoloration of the external surface. The organs contracted normally on being emptied. The urine contained a few red cells and was sterile. The bladder showed a very few small petechiae beneath the mucosa. Microscopically, nothing else was found, the vesical muscle, the ureters and the kidney pelves being normal.

EXPERIMENTS 27-28.—In two dogs of 19 and 22 Kg. the operative procedures were identical with those in the foregoing experiments. There was no leakage of urine. Ninety-six hours after operation the nonprotein nitrogen of the blood was normal. The bladders were exposed. That of dog 27 contained 1,800 cc. of turbid, sterile urine at a tension of 23 cm. Its abdominal surface was slightly cyanotic but cleared when the bladder contracted on being emptied. The urine contained a moderate number of red blood cells. There were numerous petechiae in the vesical submucosa, but none in the muscularis. The kidneys and ureters were normal.

The observations in experiment 28 were similar to those in the preceding experiment. The bladder contained 2,150 cc. at a pressure of 15.5 cc.

Comment.—It seems clear, from the degree of distention seen and from the duration of these experiments, that simple stretching of the bladder wall for periods as long as four days does not suffice to cause severe damage to the vessels of the organ. However, on the fourth day damage begins.

The chief factor in the injury to the bladder was evidently the abnormal pressure generated therein during urinary retention. The effect of rapidly developed high pressures was tested in experiments 29, 30, 31 and 32.

EXPERIMENTS 29-32.—In four normal male dogs of 12, 16, 21 and 22 Kg. the bladder was distended rapidly through a fiber catheter, under ether anesthesia. The pressure was read after the injection of every 100 cc. of sterile physiologic solution of sodium chloride. Each injection required about three minutes. A small sample of fluid was aspirated from the bladder after each injection.

In each instance, when the resultant intravesical tension exceeded from 50 to 60 cm. of water (corresponding to an average content of 400 cc.), blood appeared in the samples of irrigating fluid. Examination of the bladder wall after the appearance of bleeding showed numerous petechial hemorrhages in the mucosa and submucosa. If the distention was continued beyond this pressure, bleeding increased and the muscularis became somewhat hemorrhagic, but no gross or microscopic lesions of the kidney or ureter developed.

Comment.—Slow distention of the urinary bladder produced hemorrhages into the bladder wall within forty-eight hours. Gangrene and perforation followed in from sixty to seventy-two hours. Section of the spinal cord inhibited the development of these lesions so that at ninety-six hours (four days) only submucosal hemorrhages were seen,

in spite of a tremendous distention of the organ. The evidence of series 4 shows that distention beyond a certain pressure causes hemorrhage. Is this due to stretching or to pressure? This question is answered by series 5.

In series 5 the effect of high intravesical pressure without stretching of the bladder wall was studied.

EXPERIMENTS 33 to 36.—In normal male dogs weighing from 15 to 21 Kg., the bladder was exposed under ether anesthesia and sugical asepsis and enclosed in a sterile bag of heavy, inelastic cloth having a capacity of 150 cc. Rapid distention of the bladders was carried out as outlined earlier. It was found that elevation of the pressure above 50 to 60 cm. of water produced mucosal and submucosal hemorrhages, and that these invaded the muscularis if the pressure was carried high enough.

COMMENT

Acute urinary retention causes bleeding into the tissues and cavities of the urinary tract. The factors which produce the bleeding require analysis.

As has already been noted, interference with the venous return was long ago blamed for the congestion and venous stasis in the entire urinary tract in prostatic hypertrophy. The same factor was regarded by Cohnheim [48] as responsible for the stasis of blood in the kidney following experimental ligature of the ureter. Lindemann [49] found that obstruction of the ureter increased the volume of the kidney; Lucas [50] and Newman [51] observed a diminution in the flow of blood from the renal vein during distention of the renal pelvis; and Hinman [52] showed

48. Cohnheim, J.: Vorlesungen über allgemeine Pathologie, Berlin, A. Hirschwald, 1880.

49. Lindemann, W.: Ueber die Wirkung der Gegendruckerhöhung auf die Harnsekretion, Beitr. z. path. Anat. u. z. allg. Path. **21**:500, 1897.

50. Lucas, D. R.: On the Intraureteral Pressure and Its Relation to the Peristaltic Movements of the Ureter, Proc. Soc. Exper. Biol. & Med. **2**:61, 1904; Studies of the Peristalsis of the Ureter in Dogs by the Graphic Method, Am. J. Physiol. **17**:392, 1906-1907.

51. Newman, D.: Residual Urine and the Senile Bladder, Glasgow M. J. **87**: 73, 1917.

52. Hinman, F., and Morrison, D. M.: Experimental Hydronephrosis, J. Urol. **11**:435, 1924. Hinman, F., and Hepler, A. B.: Experimental Hydronephrosis; Effect of Changes in Blood Pressure and in Blood Flow on its Rate of Development; Partial Obstruction of Renal Artery; Diminished Blood Flow; Diminished Intrarenal Pressure and Oliguria, Arch. Surg. **11**:649 (Nov.) 1925; Experimental Hydronephrosis; Effect of Changes in Blood Pressure and in Blood Flow on Its Rate of Development, and Significance of Venous Collateral System; Partial Obstruction of Renal Vein Without and With Ligation of All Collateral Veins, ibid. **11**:917 (Dec.) 1925; Experimental Hydronephrosis; Effect of Ligature of One Branch of Renal Artery on Its Rate of Development; Simultaneous Ligation of Posterior Branch of Renal Artery and Ureter on Same Side, ibid. **12**:830 (April) 1926.

conclusively that hydronephrotic atrophy is the result of compression of the renal vessels by the distended pelvis.

This same factor appears to be responsible for the stasis of blood and later for the hemorrhage seen after occlusion of the urethra. This is shown by the congestion and cyanosis of the bladder wall, which appeared in every obstruction and which, in all except the most advanced cases, disappeared when the viscus was emptied. Further evidence is found in the location of the earliest as well as the most advanced hemorrhages in the advanced cases. They always appeared in and about the midline of the posterior wall above the trigon. Even a casual inspection of the dog's bladder shows that the blood supply is poorest at this point, a fact which indicates that a relatively slight increase in tension tends to cause damage. While these changes were attributed by Guyon and Albarran [22] to a reflex, such an explanation seems superfluous.

If urinary retention is long continued, certain secondary effects appear and aggravate the primary lesions. The first is necrosis, apparently due to deficient oxygenation secondary to interference with the blood supply by the hemorrhages; this appears within forty-eight hours and within from sixty to seventy-two hours is often sufficiently advanced to cause rupture.

The other secondary effect is functional. As has been pointed out by Guyon and Albarran, in acute retention the irritability of the bladder muscle is soon lost. In this series it disappeared in most of the experiments of forty-eight hours' duration and in all of those of from sixty to seventy-two hours' duration (experiments 10, 11, 12 and 17). It is not even then irreparable, as shown by the recovery of animals 18, 19 and 20.

These secondary effects (the first doubtless causes the second) appear to be responsible for the increased susceptibility to infection of the obstructed urinary tract. The necrotic tissue furnishes a culture medium the surface of which is isolated from the usual defenses against bacterial invasion; the loss of contractility causes incomplete emptying of the bladder. The resultant stasis favors bacterial growth.

Although a few hemorrhages in the bladder wall may appear within twenty-four hours, the kidneys are not involved for another day. This lag is undoubtedly due to the fact that reflux up the dog's ureter does not occur (Sampson,[53] Lucas,[50] Newman,[51] Draper and Braasch,[54] Bush

53. Sampson, J. A.: Ascending Renal Infection with Especial Reference to the Reflux of Urine from the Bladder into the Ureters, Bull. Johns Hopkins Hosp. **14**:334, 1903.

54. Draper, J. W., and Braasch, W. F.: The Function of the Ureterovesical Valve, J. A. M. A. **60**:20 (Jan. 4) 1913.

and McCradie,[55] Gruber,[56] Shigematsu [23] and others). The kidneys are thus protected for a time. Since the kidney and ureter together, however, may exert pressures of from 40 (Heidenhain [57]) to 76 mm. (Gottlieb and Magnus [58]) of mercury (54 to 103 cc. of water), and since the ureter alone may sustain a pressure of 67 mm. of mercury (92 cc. of water), a rise of tension in the bladder is soon met by a similar rise of tension in the ureter. Elevation of the intravesical tension is at first delayed by the tendency of the bladder (observed by Mosso and Pellacani,[47] Sherrington,[59] and others) to maintain a constant pressure regardless of the degree of distention (postural tone, Sherrington). This protective mechanism apparently fails at some time between twenty-four and forty-eight hours, when the intra-ureteral and intrapelvic tensions become sufficient to cause venous (and perhaps arterial) compression, at first with stasis and later with hemorrhage. This hemorrhage into the kidney may cause serious anatomic (figs. 2 and 4) and functional impairment, the latter being shown by definite rises in the nonprotein nitrogen of the blood in experiments 6, 7, 8 and 10.

That the hemorrhagic lesions of the bladder are due to interference with the blood supply by the intravesical tension rather than to simple stretching and tearing seemed probable from the fact that the same lesions appeared later in the renal parenchyma where the degree of distention was probably insufficient to cause actual lacerations. This view was substantiated by the results of series 4 and 5, in which it was found that if efforts to urinate were prevented, great distention of the bladder did not damage that organ until the fourth day, at which time there were mild lesions. When one compares this with the fact that much less severe distention ruptured the bladder within seventy-two hours if the animal was allowed to strain, it was obvious that pressure, not stretching, damages the bladder wall. Final proof was obtained by subjecting the bladder to high pressure by the rapid injection of fluid, both under normal conditions and while it was enclosed in a small, inelastic bag which prevented stretching. Both procedures caused changes identical with but less extensive than those due to ligature of the urethra. The greater severity of the lesions of urethral ligature were doubtless due to the much longer duration of the latter.

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55. Bush, A. D., and McCradie, R. S.: Competency of the Ureterovesical Valves, Am. J. Physiol. **68**:107, 1924.

56. Gruber, C. M.: The Function of the Ureterovesical Valve and the Experimental Production of Hydronephrosis, J. Urol. **23**:161, 1930.

57. Heidenhain, R.: Die Harnabsonderung, in Hermann, L.: Handbuch der Physiologie, Leipzig, F. C. W. Vogel, 1881, vol. 5, pt. 1, p. 299.

58. Gottlieb, R., and Magnus, R.: Ueber Diurese, Arch. f. exper. Path. u. Pharmakol. **45**:223, 1901.

59. Sherrington, C. S.: Postural Activity of Muscle and Nerve: III. Visceral Muscle, Brain **38**:213, 1915.

No attempt was made to follow the fluid output during retention, as was done by Guyon and Albarran, because, as has already been pointed out, the fluid output of dogs is irregular even when the intake of water and food is constant.

The lesions of experimental acute retention are strikingly similar to those which have been attributed by many writers to sudden emptying of the chronically distended bladder. The hemorrhages, the hematuria, the renal insufficiency and the suppression of urine (Guyon and Albarran) are seen in both. These same changes can also follow acute pyelonephritis. I have shown that patients who die after catheterization die of infection, and that gradual emptying does not reduce the percentage of infective lesions or influence the mortality in similar groups of cases. Is it necessary, then, to retain the old belief that sudden emptying of the distended bladder is dangerous? I think not.

No effort has been made in this study to ascertain by what mechanism the rise in tension which damages the bladder is produced. The literature states that the contraction of the bladder wall produces the increased tension, but it is not certain whether this is wholly true. Certain observations made in the course of these experiments suggest that it is not. For example, in experiment 3 a retention of 800 cc. produced slight changes within twenty-four hours. In experiment 4 retention of the same amount caused more severe damage in forty-eight hours. Dog 3 weighed 5 Kg. less than dog 4 and was therefore relatively more distended. Furthermore, in experiment 10 a retention of 300 cc. caused advanced changes in seventy-two hours.

Aside from the important elements of time and degree of distention, there seems to be another factor which is responsible for the fact that a given retention in one animal may cause advanced changes, while in another it has only a slight effect. The response of smooth muscle to a given stimulus is so uniform as to lead one to seek some other explanation of the varying effects of urinary retention. This explanation is probably to be found in the influence of the contraction of the abdominal wall and the diaphragm (i. e., the voluntary attempts to urinate) on the bladder pressure. The influence of this factor on pressure in the normal bladder has been recognized by Mosso and Pellacani,[47] Dubois,[60] Adler,[61] Hirsch,[62] Kreutzmann, Rose [5] and others, but no attempt has been made to separate its effect in urinary retention from that of the

60. Dubois, P.: Ueber den Druck in der Harnblase, Deutsches Arch. f. klin. Med. **17**:148, 1876.

61. Adler, A.: Ueber den Druck in der Harnblase zugleich ein Beitrag zur Funktion des Blasenmechanismus, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **30**:487, 1918.

62. Hirsch, E. W.: Relation of Bladder Pressure to Bladder Function, J. A. M. A. **91**:772 (Sept. 15) 1928.

contraction of the bladder wall. The question has been investigated, and observations will be reported in a subsequent study.

I have thus far had the opportunity of treating ten patients with marked vesical distention due to prostatic disease. The youngest patient was 50; the oldest, 78. One had a prostatic carcinoma; two had fibrous contractures secondary to prostatitis, and seven had prostatic hypertrophy. Four had incontinence (overflow): three of three months' duration and one of a year's duration. Residual urines varied from 750 to 1,500 cc.

In all, abrupt emptying was practiced, in three with the catheter and in seven with suprapubic cystostomy. In four bleeding developed after a definite latent period and was associated with the development of bacteriuria and other evidence of pyelonephritis. In the others infection and bleeding were present on admission, the latter usually being due to previous catheterization; that it preceded the catheterization in the hospital was proved by the appearance of blood in the first drops of urine evacuated and by the presence of dark, clotted blood.

One patient so nearly reproduces experimental conditions as to deserve description in detail.

CASE 4.—C. G., a man, aged 69, had increased vesical irritability for several years. Twenty-four hours before admission he had acute retention. His physician made an unsuccessful attempt at catheterization, and then referred him to the hospital, where he arrived with a distended bladder. The prostate was moderately enlarged. Blood was dripping from the urethra. Attempts were made to pass first a soft rubber, and then a filiform, catheter. These failed. Suprapubic drainage evacuated 750 cc. of urine containing dark clots. Culture showed a gram-positive bacillus. The external surface of the bladder wall was a dusky, bluish red. The temperature remained normal for six days, and then rose to 103 F. for two consecutive days, following which it returned to normal. The patient was sent home with an apparatus for suprapubic drainage and asked to return later for treatment of the obstructing prostate.

In this patient, all three of the factors sharing responsibility for bleeding in acute urinary retention, namely, prolonged complete retention, trauma and infection, were present. The bleeding cleared up promptly with free drainage. Treatment of the obstructing gland was deferred because the striking similarity in the appearance of the bladder of this patient to that of the dog with experimental retention suggested that considerable necrosis had occurred.

One experiment that would probably settle permanently the question whether sudden emptying of the distended bladder can of itself produce bleeding has not been performed. It consists of measuring the actual loss of blood in a series of patients who have been relieved or of measuring urinary retention by the indwelling catheter or by a suprapubic tube without any attempt at gradual decompression, and in comparing the amount to that in a similar series in which gradual

decompression has been practiced. This can be done by removing the blood from the urine with the centrifuge and converting the hemoglobin to acid hematin, from which the volume of blood actually lost can easily be reckoned.

Because of the relatively infrequent admission of suitable cases to a small urologic service, the investigation of this subject will require a number of years.

SUMMARY

The literature bearing on the relationship between hematuria and urinary retention as well as infection in the urinary tract has been briefly reviewed. It has been pointed out that the inconstancy of the occurrence of hematuria following sudden emptying of the bladder suggests that some factor other than the mechanical one of sudden emptying must be involved. It has been pointed out that in fatal cases the lesions following gradual catheterization are identical with those developing after sudden emptying, and that the mortality for sudden emptying of the bladder is almost identical with that for gradual withdrawal. These facts suggest that the rate of emptying of the distended bladder may not be responsible for the train of events which sometimes follows catheterization and of which hematuria is usually described as typical.

It has also been pointed out that trauma and infection may play important rôles in postcatheterization bleeding. Illustrative cases and two experiments with animals have been cited.

A series of thirty-six experiments on dogs has been performed and has shown that:

1. Acute retention interfered with the venous return from the urinary tract. This effect was seen earliest in the bladder, where it led to hemorrhage and necrosis in the area of poorest blood supply.

2. The upper urinary tract was at first protected both by the tendency of the bladder to relax as it fills and by the absence of reflux of the urine into the ureters.

3. Between twenty-four and forty-eight hours after the establishment of retention the pressure in the bladder became elevated. The kidney and ureter then generated pressures sufficiently high to impair their own blood supply.

4. It has been shown experimentally that the critical factor which leads to injury of the bladder wall during urinary retention is not the stretching with tearing of the vessels but the rise of pressure, which may be quite independent of the volume of urine.

5. The venous stasis and hemorrhages into the upper urinary tract led to impairment of the renal function after a latent period of twenty-four hours.

6. Sudden relief of the obstruction did not of itself produce lesions but led to recovery.

7. The varying intensity of lesions produced by a given degree of distention or by distention for a given period suggested that some mechanism less constant than the contraction of the bladder wall produced the rise in intravesical tension. This appeared to be the action of the diaphragm and abdominal muscles (attempts to void). A study of their relative rôle has been made, and it will be reported in part II of this paper.

8. A series of ten cases of retention due to prostatism in which ill effects did not follow sudden withdrawal of the urine by catheter (three cases) or by cystostomy (seven cases) has been reported. Hematuria occurred but could be explained adequately in each case by infection, trauma, retention or a combination of these three factors.

CONCLUSIONS

1. Experimental acute urinary retention in the dog causes venous stasis in the bladder with secondary hemorrhage, impairment of function and necrosis. The necrosis leads to rupture of the bladder in from sixty to seventy-two hours.

2. The effect on the kidney appears in about forty-eight hours and consists of hemorrhages into the wall of the pelvis and the interstitium of the kidney with resultant functional impairment.

3. Sudden relief of the retention at any time before the bladder ruptures does not aggravate the lesions but results in recovery.

4. Hematuria may also be produced by infection (cystitis or pyelonephritis) or instrumental trauma.

5. A combination of any or all of these factors suffices to account for the hemorrhages seen after sudden emptying of the bladder.

6. In a small series of patients (ten) treated by me, sudden withdrawal of the retained urine caused no ill effects. The small amount of bleeding is easily explicable as the result of infection or trauma or as the effect of the retention itself.

7. It is unnecessary to assume that sudden emptying of the bladder is responsible for the bleeding which often follows.

A REVIEW OF UROLOGIC SURGERY

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(*Concluded from p. 808*)

PROSTATE GLAND

Resection.—Legueu and Dossot [32] stated that the neck of the bladder is the seat of very diverse lesions all of which end in the same trouble—deficiency of its opening at the time of urination. The rational treatment of this condition is, therefore, destruction or section of the neck and of the relaxed sphincter. Section can be done through the open bladder. When dealing with macroscopic hypertrophy, whether adenoma or carcinoma, the endoscopic route should not be used.

The authors stated that it is illogical to attack a carcinoma of the prostate gland by the urethral route in the hope of opening a passage for urine. This is similar to attempting to treat neoplastic stenosis of the pylorus by destroying the carcinomatous buds with a curet.

The authors further stated that in dealing with microscopic lesions, whether hyperplasia of the neck of the bladder, an inflammatory process, a congenital lesion or a lesion of the nerves, good results can be obtained by endoscopic methods.

Dorman [33] reported that the first 30 transurethral prostatic resections that he performed were carried out without a fatality, except that some patients died later as a result of carcinoma. His thirty-first and thirty-second patients died. He stated that patients who know of transurethral

32. Legueu, Felix, and Dossot, R.: The Endoscopic Treatment of Dysectasis of the Vesical Orifice, Urol. & Cutan. Rev. **37**:32 (Jan.) 1933.

33. Dorman, H. N.: Personal Observations in Prostatic Resection, J. Urol. **29**:361 (April) 1933.

resection choose this operation rather than prostatectomy. Physicians who have had an opportunity to see a transurethral resection properly performed are impressed with the speed and the simplicity of the operation, the lack of danger accompanying it and the astounding immediate results.

Dorman explained the simplicity of the procedure. It is easy for the patient in comparison with prostatectomy. No operation that the urologist is permitted to perform requires more careful attention to a multitude of details, more care and skill in the actual performance of the operation and more meticulous postoperative care than transurethral prostatic resection. The urologist who is fitted by previous training and by temperament to undertake this work can offer his patient something really worth while that the prostatectomist never can duplicate, something that suffering humanity sorely needs and something that will incur the everlasting gratitude of patients.

Ryall and Millin [34] described their prostatic excisor. This instrument differs little from the resectors used in the United States. It has a straight endoscopic sheath, a loop electrode worked by a rack and pinion and a direct vision telescope. Instead of the loop alone moving on the rack-and-pinion mechanism, the telescope and lamp also do so. In this way the loop is visualized with identical illumination and magnification throughout the whole of its excursion. Moreover, almost the whole of the loop is visible, so that during cutting when the lower portion of the loop is embedded in tissue the upper part is clearly seen. The whole procedure is thus visualized. The authors stated that with the armamentarium now available it is feasible to resect as much prostatic tissue as they please. Although agreeing with McCarthy and others that it is often sufficient to gutter the posterior commissural region and establish a shelving floor, they prefer when possible to resect widely, attacking the lateral lobes also. When a very large gland is to be treated, they choose to operate in two stages rather than to subject the patient to a procedure lasting more than forty-five minutes. The indwelling urethral catheter is retained for the five to seven days that elapse between the two stages, as the coagulated area in an imperfectly emptying bladder predisposes to an ascending infection.

Ryall and Millin stated that they found that transurethral resection as applied to malignant growths of the prostate gland, although frequently a most satisfactory procedure, causes more prolonged postoperative discomfort than it does in cases of benign enlargement of the gland. The sloughs take longer to separate. Probably not more than 5 per cent of obstructions of the prostate gland could not be dealt with by transurethral resection, but the authors feel convinced that it is

34. Ryall, E. C., and Millin, Terence: Endoscopic Resection of the Prostate: A Survey, Urol. & Cutan. Rev. **37**:52 (Jan.) 1933.

undesirable to apply the procedure in more than 75 per cent of the cases. In early cases it is probably of great prophylactic value. In the advanced "bad risk" case, in which prostatectomy is contraindicated even after prolonged drainage, transurethral resection has a very definite place. As the authors stated, resection in two stages may be indicated in cases of very large obstructions in the gland, and it is their practice to employ a temporary suprapubic tube in some cases of this type in which infection in the urinary tract might well tip the scale. For relatively young men who have considerable enlargement of the prostate gland and whose cardiovascular and renal function is good, Ryall and Millin prefer suprapubic enucleation unless this is otherwise contraindicated. The expectation of life of such a patient is usually reasonably long, and the rapid development of the hyperplastic process suggests "exuberance"; therefore a recurrence may develop within a short time after resection.

Ryall and Millin almost invariably employ a "low spinal anesthesia." From 6 to 10 cc. of 1 : 500 nupercaine in 0.015 per cent saline solution warmed to body temperature and introduced intrathecally gives excellent analgesia of sufficient duration for any form of resection. In their experience, sacral analgesia is less reliable and its administration is no less unpleasant for the patient. They have carried out transurethral resection on 73 patients with but a single death, and in that case there was a malignant growth. Excluding 6 cases of malignant growth, 67 benign enlarged glands were resected without causing a death. There was no selection of cases, and in no case was resection refused. The ages of the patients varied from 54 to 88, and in some instances the blood urea content was as high as 136 mg. in each 100 cc. after drainage for three months. In only 3 cases was cystotomy necessary subsequently. These 3 accidents occurred in the first 13 cases, when the authors were working with a varying technic. Since then resection has been carried out in 60 cases without an unfortunate incident.

The authors concluded that endoscopic resection of the prostate gland deserves a definite place in urologic surgery. It calls for the highest degree of technical skill and if carelessly used may lead to disaster of the greatest magnitude.

Luys,[35] of France, stated that since the discovery of electrocoagulation and of its practical application in the field of urology, he has at last been able to establish the operation which he calls "forage of the prostate" and to make it both practical and completely effective. This operation consists of hollowing out a channel through the hypertrophied prostate gland by way of the natural passages and by means of electro-

35. Luys, Georges: The Endoscopic Surgery of the Vesical Orifice, Urol. & Cutan. Rev. **37**:34 (Jan.) 1933.

coagulation under direct vision. A tunnel is formed to permit a free outlet for urine by the removal of all obstacles which interfere with urination. From this definition it is evident at once that forage of the prostate gland is a much more extensive intervention, and much more radical and complete, than simple endoscopic resection. It destroys all the obstacles which obstruct urination, whether situated at the vesical orifice or in the prostatic urethra. It levels all prostatic protuberances and furnishes an absolutely straight canal, through which not only do sounds pass easily but the patient is able spontaneously to urinate and empty the bladder.

The author stated that various other methods described by different urologists have the same principal fault; namely, they are incomplete. First, because they attack only the vesical orifice, they are unable to destroy the prostatic obstruction totally, and second, because they apply the destructive agent, which is electric heat, under water, they diminish its power of action considerably. Luys' so-called forage of the prostate gland destroys all prostatic obstructions and has a thermic destructive action infinitely more powerful than that of other methods because it operates in a dry field without the intervention of water.

Forage of the prostate gland consists of repeated coagulation of sections of the obstructing gland at repeated sittings, the manner of application being similar to simple fulguration of a vesical tumor. The burned area is then left to slough out. A warning was given to beware of hemorrhage. Luys concluded that forage of the prostate gland, properly performed, gives perfect and lasting results, and that the operative mortality may be regarded as zero.

Joseph [36] stated that transurethral resection of the prostate gland still hides a considerable amount of danger, the mortality not being notably less than that resulting from the now technically perfected operation of prostatectomy. Therefore, he cannot make up his mind to employ to any great extent the instruments constructed in the United States for diminishing the size of the prostate gland, as he considers the danger of bleeding and sepsis, especially perforation, to be just as great as the danger involved in a modern prostatectomy. If the patient on account of advanced age and poor general condition appears unsuitable for prostatectomy, Joseph recommends either permanent suprapubic drainage or vasectomy.

[COMPILERS' NOTE.—Joseph's remarks reflect the opinion of a group of continental surgeons who were prominent from twenty to thirty years ago. Their former indifferent opinion of the skill and technic of

36. Joseph, Eugene: The Present Position of Endoscopic Operations in Prostatic Hypertrophy and Prostatic Atrophy, Urol. & Cutan. Rev. **37**:59 (Jan.) 1933.

American surgeons has been greatly altered in the last ten years. Unquestionably, the reports of cases of transurethral prostatic resection, if read by Joseph, deserve a more favorable review. Transurethral resection of the prostate gland is practiced in London to a certain extent, and the instruments are modeled after those used in this country. The operation is practically not done in continental countries. In the various discussions at the recent International Urological Congress, the operation was favorably commented on by English surgeons but either was not discussed or was commented on unfavorably by the urologists of France and Germany.]

Bumpus [37] stated that prostatectomy has been performed at the Mayo Clinic only 3 times since August, 1932. In the same period approximately 250 patients were treated transurethrally. This new method of treating prostatic obstruction has increased the work in this field to such an extent that more patients with prostatic obstruction were treated during 1932 than in any other year of the clinic's history, and of the 276 patients on whom transurethral resection was performed none died. The decrease in mortality among aged patients is most gratifying, as is also the short period of convalescence, which is usually about one week in the hospital.

In addition to shortening the postoperative course of the disease, this method has diminished the time required for preoperative preparation. It has long been the belief that preliminary drainage of the bladder can improve a patient's condition only if marked renal impairment secondary to obstruction has occurred or if considerable urinary infection is present. If these two conditions are absent, it does not seem logical that preoperative drainage can be of any service; in fact, such drainage may result in a much poorer surgical risk, for when undertaken in the absence of infection it often has produced infection. Therefore, 44 per cent of the patients were operated on immediately after the diagnosis was made, and the satisfactory postoperative course demonstrated that this departure from a long established precedent was justified.

Bumpus stated that in almost all of 499 cases in which this procedure was used in the last six years, there was residual urine before operation, in large amounts in some instances. After operation, on the other hand, more than 300 patients had no residual urine; 40 had from 1 to 30 cc.; 20 had from 30 to 60 cc., and very few had more than 60 cc. In this group there were 7 deaths—a mortality of 1.4 per cent. Two hundred and ninety-one consecutive patients were operated on without any deaths. Some doubt has been expressed as to the permanence of this form of treatment. Among this group of 499 patients the condition has

37. Bumpus, H. C., Jr.: Transurethral Surgery, Proc. Staff Meet., Mayo Clin. 8:204 (April 5) 1933.

been known to recur 11 times. Two patients were relieved by subsequent prostatectomy, and 9 underwent resection a second time. Even in repetition this procedure seems preferable to prostatectomy.

Bumpus expressed the belief that the instrument developed by him, a tubular knife with which the tissue is excised, gives better results than the wire loop electrode which was used on about 50 of these patients. Excision with a cold knife results in much less coagulation of tissue than does excision by means of a high frequency current, and therefore less coagulated tissue is left to act as a secondary source of infection or to produce delayed bleeding by the late breaking away of the scar. Moreover, in his experience, an incised wound heals more rapidly than a cauterized wound. Although bleeding in a more or less severe form was a complication of convalescence in 5 per cent of the cases, it was never a contributory cause of death; it usually can be easily controlled cystoscopically if the patient has not left professional observation.

Bumpus stated that the largest amount of tissue removed so far by this method weighed 63 Gm. Considering the fact that probably not more than a fifth of the hypertrophied gland has to be removed to restore adequate function, the ability to remove this amount of tissue bears testimony to the general applicability of the method. In 575 recent consecutive cases in which prostatectomy was performed, only 32.1 per cent of the removed specimens weighed more than 50 Gm.

Foley [38] discussed the instrument that he uses and his methods of removing obstruction from the neck of the bladder. The sheath and the working elements of his instrument are introduced through the urethra. The tip of the instrument, containing the light, can be turned to a right angle; from the extreme tip a cutting wire passes down to the shaft of the instrument. Traction on this electrode wire bends the deflecting arm of the lamp down to a point at which it illuminates the vesical neck. The cystoscopic field of the telescope gives a mirror image of the object. Several radial incisions are then made into the body of the prostate gland. In making these incisions the electrode conduit is slid down the telescope to a point of sufficient travel to make the necessary cut. The lower end of the cutting element is thus carried down into the urethra and the upper end is projected toward the periphery of the gland, and its length cuts back into the gland. After a number of these radial incisions are made, the instrument is rotated. Rotation of the instrument progresses from one of the radial incisions past the one next to it, so that the block of tissue between the two is completely severed from attachment. By further

38. Foley, F. E. B.: The New Surgery of Bladder Neck Obstruction, Urol. & Cutan. Rev. **37**:17 (Jan.) 1933.

rotation of the instrument in the urethra, the incision is completed. The segments which are removed by this method are usually from four to ten times the size of those removed by other instruments. Foley stated that for dealing with bars, contractures and small hypertrophied glands, the new type punch instruments in ordinary usage at present are entirely satisfactory. In cases of extensive enlargement, the punch type of instrument presents considerable disadvantage. This disadvantage is practically eliminated by the Foley excisor.

Herbst [39] stated that it would be difficult at this time to determine all the indications for electroresection. There is little question but that it will replace operations with punch instruments. In the short period in which it has been used, it can be fairly stated that it is the operation of choice in cases of moderate hypertrophy of the lateral lobe, of hypertrophy of the middle lobe, of formation of median bars and of fibrosis of the neck of the bladder. Whether it will prove to be a practical procedure for the correction of intrusions of the large lateral lobe is a question which only the future can answer. Herbst expressed the belief that it is a fair assumption that men who have become skilled in this method are today using it in at least 75 per cent of cases of urinary obstruction caused by the prostate gland.

Winsbury-White [40] contended that transurethral resection of the prostate gland will not replace prostatectomy and that its use should be limited to cases of fibrous obstruction.

Perineal prostatectomy has had little vogue in Great Britain, largely because the exponents of the suprapubic operations have had no experience with it and because of the unwarranted fear of postoperative urinary incontinence. This can be obviated by proper technic. White described the method that he employed in 40 of 60 perineal operations to avoid this complication. The important features of the technic are preliminary suprapubic cystostomy with preservation of the prostatic capsule to be sutured over the reconstructed urethra and anastomosis of the stump of the divided urethra to the neck of the bladder; the resutured prostatic capsule is secured firmly to the perineal muscles lying superficial to the compressor urethrae muscle in order to provide support for the new posterior portion of the urethra and the readjusted vesical base. In this way the prostatic space is obliterated and large scars are avoided.

Winsbury-White has devised several instruments to facilitate this procedure. He uses for drainage in suprapubic cystostomy an indwelling catheter and a perineal tube which does not enter the bladder.

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39. Herbst, R. H.: Electro Resection of the Prostate Gland, Urol. & Cutan. Rev. **37**:64 (Jan.) 1933.

40. Winsbury-White, H. P.: Perineal Prostatectomy, Brit. J. Urol. **5**:113 (June) 1933.

Secondary hemorrhage is rare. In 2 cases it was necessary to remove a few sutures and to wash the clots through the perineum. Recto-urethral fistulas occurred twice and were avoided in 2 other cases by performing suprapubic enucleation after the rectum was opened but before the opening of the urethra.

The author prefers prostatectomy in two stages to suprapubic prostatectomy, with which he has had considerable experience, because it is easier to stop hemorrhage, there is less operative shock, complications due to infection are fewer and convalescence is smoother and less eventful.

Day [41] stated that transurethral resection is here to stay. With continued and increased experience, and with perfection of instruments and of technic, some of the major worries and fears have been largely overcome, and dangers and deficiencies have in a measure been brought under control if discretion is observed. The author stated, however, that in huge adenomatous prostate glands, resection is both unsatisfactory and needlessly dangerous.

Chetwood [42] expressed the opinion that endo-urethral resection of the prostate gland in accordance with the modern technic is a valuable and efficient procedure in many cases of obstructing prostate gland. He stated that the types of obstruction for which this technic is best suited are the fibrous or fibro-adenomatous enlargements of the gland and the bar and lobe formations of minor degree, removal of which can be completed without too great destruction of tissue or too long an operation. The open operation of prostatectomy is best suited to some cases of prostatic obstruction, particularly those with pronounced lobular, bilateral and median enlargement of the gland; in these cases, with proper preparation the skilled operator attains a low degree of mortality and a promise of a permanent and satisfactory end-result. The combined operation of suprapubic incision and removal of tissue by a diathermic excisor may be appropriately applied in cases in which direct vision and drainage are important factors.

Davis and Owens [43] stated that transurethral resection of the prostate gland, properly employed in selected cases, is undoubtedly a valuable procedure. The majority of surgeons believe that this operation will partially replace, but not supplant, prostatectomy. The immediate results of transurethral resection in selected cases seem to be satisfactory. The ultimate results can be determined only by time. The chief advantage

41. Day, R. V.: Transurethral Resection of the Prostate, Urol. & Cutan. Rev. **37**:50 (Jan.) 1933.

42. Chetwood, C. H.: The Obstructing Prostate, Urol. & Cutan. Rev. **37**:44 (Jan.) 1933.

43. Davis, Edwin, and Owens, C. A.: Prostatectomy and Transurethral Prostatic Resection Compared, Nebraska M. J. **18**:41 (Feb.) 1933.

offered to the patient by the transurethral method is a decreased period of hospitalization. Preliminary drainage, however, is just as essential as before prostatectomy. It seems doubtful to the authors whether, in the last analysis, considering the mortality rate and the immediate and the ultimate functional results, the transurethral method offers the patient as great a degree of assurance of continued health and comfort as does perineal prostatectomy.

Lewis and Carroll [44] gave a timely warning against too great enthusiasm for transurethral resection of the prostate gland. They stated that from reports of the experience of capable operators in various parts of the country it may be deduced that it is not only erroneous but dangerously misleading to teach that resection is a "minor" operation. At present, it has not reached a state of perfection that justifies the assertion that it will supplant prostatectomy. It is the responsibility of the operator to draw the line of demarcation between the patients that are fit and those that are unfit for undergoing resection, maintaining an open mind to the advantages and the disadvantages, as well as the appropriateness, of each operative method.

Caulk,[45] after a careful scrutiny lasting over a period of twelve years, stated that he was convinced from his observation of the cases in which operation was performed with punch instruments that transurethral resection can be effectively employed for the removal of at least 80 per cent of all prostatic growths, benign or malignant, and that it can be used for the removal of growths of immense dimensions. He stated, however, that in the case of very large growths, if the patient presents a good surgical risk it is wiser to remove the growth surgically, since it requires more time to relieve the obstruction by transurethral means. If the patient is young and in good condition, the chance of a fatal result of prostatectomy is slight; but old patients present a poor surgical risk, and if time is not to be considered the transurethral method is the operation of choice. It must be performed by repeated operations rather than by extensive removal at any one time.

For years Caulk has pleaded for simplicity in transurethral operation and has advocated multiple stages; in cases in which instrumentation is short, the absorptive surface is slight, the chance of hemorrhage is minimized and the danger of complications resulting from anesthesia is practically eradicated. Extensive and prolonged transurethral operations on the prostate gland are menacing the lives of patients today more than well conducted prostatectomy has for years, and unless

44. Lewis, Bransford, and Carroll, Grayson: Prostatic Resection—Without the Moonlight and Roses, Urol. & Cutan. Rev. **37**:1 (Jan.) 1933.

45. Caulk, J. R.: The Present Status of Transurethral Surgery for the Removal of the Obstructing Prostate, Urol. & Cutan. Rev. **37**:14 (Jan.) 1933.

urologists realize the seriousness of such performances, the progress which has been slowly and substantially developing will be shattered. Caulk further stated his conviction that it is not a part of prudence to perform extensive transurethral resection with the type of drainage that can be afforded by the urethral catheter.

Caulk still feels that light searing by means of cauterization is superior to any form of resection with a high frequency current in that it is easily controlled and the depth of burning is entirely understood, and consequently necrosis and secondary hemorrhage are less likely to occur. The greatest testimony to this is that he has seen but 1 or 2 secondary hemorrhages in 800 operations.

Caulk stated that the serious feature of the transurethral method at present is the competitive struggle for supremacy on the part of the different manufacturers of instruments and the placing of such tools in the hands of the incompetent, untrained operator, who is informed that the instrument is almost fool-proof, and that any one can use it without danger. He stated that it must be realized that these operative procedures require the utmost skill and delicacy of technic, that patients need the same preparation that is required for major operations and that no unnecessary chances should be taken either in operating on unprepared patients or in working under the sublime delusion that the electrical instrument will do the job. It must be made equally impressive that the postoperative care of the patients requires the most stringent attention to detail if the ultimate purpose of operation is to be attained.

Levy and Goldstein [46] resected the prostate glands of 19 selected patients. Three died (a mortality rate of 15.7 per cent); 2 of the deaths were due directly to the operation. Ten (52.6 per cent) of the 19 patients had serious complications following the operation; 14 (73.7 per cent) claimed improvement in one form or another, and only 8 (42.1 per cent) stated that they obtained complete relief from symptoms.

The authors stated that in studies made at necropsy in 2 cases it was observed that comparatively little tissue was removed even though many sections were made. Slight scarring was visible after healing had taken place.

Sufficient preoperative care should be given the patients. The average preoperative stay in the hospital was twenty-seven and seven-tenths days, and the average postoperative stay, twenty-one and nine-tenths days. The authors stated that cystoscopy and tests for residual urine should not be carried out until four weeks after the operation; otherwise a true picture will not be obtained.

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46. Levy, C. S., and Goldstein, A. E.: Clinical and Postmortem Study of Prostatic Resections, Urol. & Cutan. Rev. **37**:55 (Jan.) 1933.

Stern [47] wrote that his purpose was not to add anything to the argument for or against the method of transurethral resection for operation on the prostate gland; it was rather to direct attention to the legitimate field of application of this method, to advise fitness of the patient as a criterion on which to base a decision to perform resection, to suggest a method for the accomplishment of the operation and, most important, to advise those entering the field concerning the complications and risks.

Lymphatic Structures.—Llorca and Botár [48] made 50 preparations of the prostate glands of human fetuses, new-born infants and children with a view to studying the arrangement of the lymph nodes of the organ. They observed that the lymphatic structures leave the prostate gland at the level of its upper and posterior parts, either following various arteries (anterovesical, prostatic, superior hemorrhoidal) or canals (vas deferens, ureter) or take a route independent of these organs. They terminate in all the ganglions of the bony pelvis, in most of the external iliac ganglions and in the inferior mesenteric ganglions. The prevenous ganglion in front of the bifurcation of the primitive iliac and hypogastric ganglions receives the greater portion of the lymph from the prostate gland. The highest ganglion with which a direct lymphatic connection exists is the lowest left para-aortic ganglion; the lowest one with which there is a connection is the median retrocrural ganglion.

After the lymphatic structures issue from the right and the left part of the prostate gland, they may cross the median line either on the anteroposterior surface of the bladder or on that of the promontory and reach the opposite side. The collecting lymphatic structures of the prostate gland communicate also with those of the rectum.

Clinical findings confirm the anatomic findings when evidence is submitted that the groups of ganglions most commonly invaded by carcinoma of the prostate gland are the hypogastric and the external iliac, after which come the para-aortic. The invasion of the last named ganglions may be direct, by way of the hypogastric and external iliac chains, which is rare, or indirect, by the visceral route through the hemorrhoidal chain, which is the usual route.

The rarity with which carcinoma of the prostate gland invades the inguinal lymph nodes may be due in part to the fact that invasion of these nodes may occur by either of two different routes: by the retrograde route from the external iliac nodes to the inguinal nodes, or by

47. Stern, Maximilian: The Stern Method of Prostatic Resection: "The Improved Resectoscope," Urol. & Cutan. Rev. **37**:7 (Jan.) 1933.

48. Llorca, F. O., and Botár, J.: Collecteurs lymphatiques de la prostate, Ann. d'anat.path. **10**:40 (Jan.) 1933.

extension of infection from the neoplasm to the perineum, the lower part of the rectum and the anterior portion of the urethra, and thence to the inguinal nodes. The great frequency of invasion of the bladder, on the other hand, is well explained by these anatomic researches. The infiltration reaches first the vesicular muscularis and later the mucosa. The authors think that this route is due to the intimate relations between the collecting lymphatic structures of the prostate gland and the muscular layer of the anterior surface of the bladder. They have also proved that these collectors frequently pass into the prevesical ganglions.

The frequent occurrence of metastasis to bone, particularly into the sacrum and the lumbar part of the spinal column, is explained better by lymphatic than by hematogenous transmission. Metastasis to bone may be secondary to the primary involvement of the presacral or of the para-aortic ganglions, which, as has been seen, receive lymph from the prostate gland and also from these bones. Here a retrograde route from the ganglions to the bony region would have to be assumed. All these considerations show the enormous difficulty involved in surgical treatment of carcinoma of the prostate gland.

Diverticulum.—Heitz-Boyer [49] stated that troubles resulting from the formation of diverticula in the prostate gland are always caused by a disproportion between the size of the orifice leading from the diverticulum into the prostatic urethra and the size of the bottom of the diverticulum itself. The variety of planes that the diverticula may occupy makes it indispensable to make three urethrograms (one anteroposterior view and two lateral profiles, one right and one left), thus giving two oblique views; an anteroposterior view alone might leave a diverticulum undiscovered. Since these formations are often multiple, in the form of a bunch of grapes, the failure to discover one of them may render useless all therapeutic attempts.

Congenital diverticula may exist but are rare. Usually these structures are acquired as the result of earlier suppurative prostatitis, often a number of years previously. A small abscess, possibly microscopic and unrecognized, constitutes the first stage. The second stage is a period of latency, lasting for five, ten or even fifteen years, until some secondary infection, perhaps from the urine, is grafted to one of these cavities, producing the third stage, namely, secondary septicemia of prostatic origin, which brings the patient to the physician. The infective agents are usually colon bacilli or enterococci, but may sometimes be staphylococci.

The local symptoms are those of cystitis, but these are accompanied by general disturbances which are often characteristic: phenomena of

49. Heitz-Boyer: Les formations diverticulaires de la prostate, J. d'urol. **36**:49 (July) 1933.

intoxication, a constant sense of fatigue and incapacity for work; in extreme cases, loss of weight, constant fever and the gravest symptoms of septicemia. The diagnosis is made by urethroscopy and urethrography; in addition, rectal palpation may reveal a more or less marked depression at the level of the cavity. For urethroscopy Heitz-Boyer uses a special instrument with a double or even a triple optical system and a double fenestra, which he regards as indispensable.

Treatment is by endoscopic resection with a high frequency cutting current, and the operation is carried out in two stages. It consists of enlarging the orifice and breaking down the partitions that separate the numerous deep ramifications, which are often difficult to destroy. The close proximity of the rectum warns the surgeon not to take any step without the most perfect visualization of the operative field. The final destruction of every honeycomb cavity may not be feasible if the patient rebels against undergoing a second operation. In such cases it may suffice to finish with curettage by cold or warm etincelage, which will disinfect the alveolar mucosa and so accomplish a clinical cure. A catheter must be left in place for at least a week. Care must be taken not to engage the tip in an immoderately enlarged diverticulum. This may be accomplished by using a Guyon sound with double curvature.

[COMPILERS' NOTE.—It is obvious that when a prostatic abscess has ruptured into the urethra the remaining cavity is almost certain to form an acquired type of urethroprostatic diverticulum.

Gutierrez and Lowsley [50] have thoroughly considered the two types of acquired and congenital diverticula which are found in the urethra. They have reported 7 such cases and have reviewed and tabulated 113 cases from the literature. There is no doubt that in cases in which there is persistent disturbance of urinary function and of the genitalia of unrecognized origin, a urethrocystogram will often disclose the presence of a concealed sac or cavity, which when it is of the retentive type represents a true pathologic and surgical entity.]

UROGRAPHY

In the course of one year, 1,216 urograms were made at the Mayo Clinic, of which 734 were made by the intravenous and 482 by the retrograde method, or a ratio of almost 2:1. The proportion of intravenous urograms is probably much larger than that observed in most clinics, and it may be asked whether this is necessary, in view of the expense involved. The clinic has been using neoiopax as the

50. Gutierrez, Robert, and Lowsley, O. S.: Diverticulos de la uretra, Rev. de med. y cir. de la Habana **33**:229 (April) 1928; Chirurgische Behandlung der Harnröhrendivertikel mit Projektion, Verhandl. d. deutsch. Gesellsch. f. Urol. **3**:312, 1929.

medium of choice because of the better visualization that it produces. The price of the drug has been reduced practically one-half. Braasch [51] stated that it was his understanding that another urographic medium is about to be put on the market which is to retail at less than $1 an ampule. Regardless of this, he stated that intravenous urography affords data which can be acquired in no other way and that undoubtedly it prevents a considerable number of unnecessary cystoscopic examinations. On the other hand, there are definite limitations to the diagnostic value of intravenous urograms, which should be clearly understood. The greatest value of the method lies in the demonstration of renal stasis, such as occurs with hydronephrosis. This condition often can be demonstrated much more clearly by intravenous urography. It is also of value in the interpretation of shadows in the region of the kidney and the ureter. In many cases of lithiasis in which intravenous urography is used, cystoscopy is unnecessary, as a complete diagnosis can be established by the former method alone. Often it is used to visualize a normal pelvic outline and to show normal renal function on the opposite side. For a number of purposes, however, such as the determination of the source of hematuria, the localization of tuberculosis and the identification of abdominal tumors, the evidence afforded is distinctly misleading. In fact, in all cases in which pyuria and hematuria are predominant, cystoscopic examination is necessary in order to exclude the bladder as the possible site of origin. In other words, the data obtained by intravenous urography and those furnished by cystoscopy are usually complementary, and the combined use of the two methods permits of greater accuracy than was formerly possible. The value of intravenous urography as a test of renal function should not be overlooked, since it often gives a better idea of differential renal function than does any other test.

Moore [52] stated that in 50 cases in which neoskiodan was employed intravenously for urography, the following advantages were noted: The substance does not cause pain on injection; it produces shadows of excellent density and detail in the urinary tract, and its intravenous administration has produced almost no systemic symptoms. The volume of solution used for injection into adults is small (20 cc.), and the quantity of the substance required is only 7 Gm. The aqueous solution is stable. So far, Moore's experience leads to the impression that neoskiodan more nearly approaches the ideal medium than any other agent developed for urography.

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51. Braasch, W. F.: Report of the Section on Urology, Proc. Staff Meet., Mayo Clin. **8**:201 (April 5) 1933.

52. Moore, Thomas D.: Excretion Urography with Neoskiodan, J. Urol. **30**:27 (July) 1933.

Swick [53] presented a recent development for use in urography, sodium ortho-iodohippurate, which has many advantages. It is inexpensive, has no toxic effects and can be administered in a small volume of diluent. A comparatively small quantity of the salt is required for satisfactory urograms. Good results have been obtained by oral administration as well as by intravenous injection.

Scott [54] stated that in the making of pyelograms great pressure of the injected medium does not enlarge the diameter of the ureterographic shadow beyond that of the normally filled ureter. Pyelovenous backflow can occur with the range of pressures ordinarily used in making clinical pyelograms. The form of the renal pelvis and the presence of disease are apparently not factors in producing this phenomenon. Occurring as it does at low pressures, pyelovenous backflow is an adequate explanation of some phenomena occurring in the pathologic physiology of ureteral obstruction and of some reactions occurring in clinical pyelography. Injection into the collecting tubules of the kidney may occur with the pressures used in clinical pyelography. It is independent of pyelovenous backflow and in the pyelogram may readily be distinguished from it and from extravasation.

Hennig and Lechnir [55] demonstrated in vitro and in vivo that thorotrast (a thorium dioxide contrast medium) is precipitated when mixed with urine. In roentgenograms of the cystic kidney, this precipitation forms shadows that have a peculiarly level upper surface. These can be recognized in the roentgenogram when the patient is standing. The authors stated that in their opinion this is the most accurate method for the diagnosis of sacculated kidney.

Sartorius and Viethen [56] made a study of the various substances in use for retrograde pyelography. The complex iodine compounds which are in general use (iopax and other preparations) are entirely satisfactory and permit a painless, nonirritating pyelogram; consequently, they were accepted by these authors as the best contrast mediums for intravenous injection. They also showed that the colloidal thorium dioxide preparation has the same advantage as these various iodine

53. Swick, M.: Excretion Urography by Means of the Intravenous and Oral Administration of Sodium Ortho-Iodohippurate: With Some Physiological Considerations, Surg., Gynec. & Obst. **56**:62 (Jan.) 1933.

54. Scott, D. E.: The Effects of Pressure of Pyelographic Mediums, J. Urol. **30**:39 (July) 1933.

55. Hennig, O., and Lechnir, J.: Spiegelbildung in Sacknieren nach retrograder Pyelographie mit Thorotrast, eine neue Darstellungsweise erweiterer Nieren, Ztschr. f. urol. Chir. **37**:60 (April 22) 1933.

56. Sartorius, F., and Viethen, H.: Klinische und experimentelle Untersuchungen zur Frage der Kontrastmittelwahl bei der retrograden Pyelographie insbesondere über die Verwendbarkeit des Thorotrastes, Ztschr. f. urol. Chir. **36**:312 (March 11) 1933.

preparations; moreover, it may be used in weaker dilutions and is therefore less expensive. It has the disadvantage, however, as has been shown on several occasions, of becoming stored in the kidney and causing trouble. This rarely happens when only slight pressure is used, but in occasional cases of extensive disease it may cause trouble.

Sporl,[57] in accounting for the dangers usually thought to be associated with the introduction of gas into the renal pelvis and the bladder, made an investigation of this procedure. He stated that it is of value in certain cases and that if a correct technic is used the introduction of gas into the renal pelvis and the bladder is comparatively harmless. He advised the following precautions: (1) substitution of oxygen for air; (2) careful control of pressure and fractional injection; (3) limitation of the amount of oxygen introduced into the bladder to 150 cc., and (4) avoidance of the use of this measure for patients who have cardiac or pulmonary disturbances.

Verrière[58] carried out experiments to discover what would become of a foreign substance (in this instance, 5 per cent india ink in the physiologic serum) injected into the renal pelvis and left in place for a certain time, with the ureter tied, during which the animal resumed its normal life. The lower end of the ureter in some cases served as the point of entrance; in others, the ink was carried directly into the pelvis or into the extremity of the urinary conduit; care was taken to avoid infection, pyelovenous reflux and excessive loss of blood.

After from half an hour to twelve days, india ink was discovered in 13 of 15 animals within the cells of the mucosa, chiefly on the papilla and at its base, and even in the uriniferous tubules. This phenomenon began half an hour after injection, attained its maximum in six hours and then progressively disappeared. In 11 cases the substance was found in the collecting tubules, and in 10, in the cells of the intermediary tubules. It could also be recognized in the venous system and in the interstitial perivascular, peritubular and peripyelic connective tissue. Evidences of it were observed too in the capsule, the lumbar wall and the ganglions. In six experiments carried out under special conditions, similar phenomena were observed in the convoluted tubules.

An attempt was then made to learn whether identical results would be obtained in hydronephrotic kidneys under the same conditions. The small number of experiments (three) makes final judgment impossible. One case had to be ruled out on account of faulty technic. In another case, in which infection was marked, there was no phenomenon except

57. Sporl, H. J.: Ueber die Zulässigkeit der Gasfüllung des Nierenbeckens und der Blase, Ztschr. f. urol. Chir. **36**:404 (March 11) 1933.

58. Verrière, Pierre: Contribution à l'étude de l'absorption intrarénale, J. d'urol. **36**:27 (July) 1933.

ascent of the ink up to the capsule in the tubules in the cortical region; in the third case, only a small number of foreign elements were found in the cells, except at the level of the pyelic mucosa, in which the picture was much like that seen in the first series. Neither rupture nor infiltration was observed, but only a minimal ascent at the level of the papilla in the tubules on the right side. In the vessels, in the perirenal region and on the lumbar wall, the conditions were like those observed in the earlier series of experiments.

In a third series of experiments, made for the purpose of discovering lymphatic routes of absorption, milk was injected on account of its fatty content. The results were striking: The fatty elements were found in the same distribution that was observed in the other series, but they were present in far greater quantity and had been carried to higher segments.

Verrière regarded it legitimate to assume that these foreign elements recognized in the blood, in the interstitial tissues of the kidney and in the lymphatic channels arrived there through absorption, passing through the cells bordering the cavities in which they had been placed. Once having entered the cells, the foreign elements evolve in the protoplasm; from the apical pole they reach the other pole, and following along the nucleus they clear the basal membrane and fall into the interstitial tissue, where they are seen gliding along the tubules and vessels.

These experiments are of practical interest in that they suggest that certain painful disturbances following pyelography with irritating substances (renal infections, abscesses of the kidney and even perinephritic abscesses) may owe their origin to this simple fact of absorption—in such cases, that of bacteria crowded into a ureter under the force of vesical contractions. The experiments also suggest that this power of absorption in the walls of the upper uriniferous elements might be utilized therapeutically.

URETHRA

Tumor.—Campbell [59] reported 2 cases of diverticulum of the urethra in boys. In each case urethral stricture existed. In the first case the sacculation followed crushing of the pelvis; in the second, Campbell believed that it followed severe trauma caused by dilation of a urethral stricture at the age of 22 months. Both cases serve to illustrate the importance of urologic examination among young persons, and indicate further that children are heirs to almost every urologic lesion that is associated with adult life.

Rupture.—Haines [60] stated that conservative treatment, such as simple cystostomy, especially in the hands of less experienced surgeons, is

59. Campbell, M. F.: Diverticula of the Urethra, J. Urol. **30**:113 (July) 1933.

60. Haines, Carlyle: Traumatic Rupture of the Urethra, J. Urol. **29**:285 (March) 1933.

a more satisfactory method of treating patients with incomplete or complete rupture of the urethra, whether in the bulbous portion or in the area posterior to it, than the more radical treatment, such as perineal section or urethral anastomosis, which so many advocate. He believes that each case is a law unto itself. No 2 patients will have identical injuries, nor will any 2 suffer the same amount of shock or have the same ability to combat it. Whether drainage by catheter, suprapubic cystotomy, perineal section, end-to-end anastomosis or a combination of all four is relied on depends entirely on the individual case, the length of time following the injury and its severity. The condition of the patient should be the guiding factor in the choice of a method of treatment.

PENIS

Tumor.—A review of 540 cases of carcinoma observed at the Siriraj Hospital, Bangkok, Siam, from 1927 to 1931 [61] showed that 52 (9.6 per cent) of the patients had carcinoma of the penis. If only the cases in men are considered, the percentage of incidence becomes 22.5. This confirms the impression of the relatively high frequency of this disease in the East.

Statistics show the complete immunity of orthodox Jews and the relative immunity of Mohammedans. This indicates that phimosis is the chief predisposing factor and that circumcision performed at birth should prevent carcinoma of the penis. Among the Siamese who are Buddhists, circumcision is not performed unless there is a definite surgical indication, and in the remote areas of that country this operation is practically never performed in childhood.

The average age of the 52 patients was 49.6 years. Half of the patients were farmers who lived in a very primitive way with poor hygienic surroundings. Their clothing was constantly wet and soiled with mud during long hours of work in the rice fields.

Phimosis was definitely present before the onset of the carcinoma in 24 cases; in 26 cases the records did not indicate clearly whether phimosis was present, and in 2 cases there was no phimosis. The Wassermann reaction was positive in 14 of 44 cases. These facts indicate that phimosis and syphilis may have a distinct bearing on the etiology of the disease.

In the 51 cases in which operation was performed, complete amputation of the penis was done in 6, complete amputation with block dissection of the lymph nodes in 8, partial amputation in 17 and partial amputation with block dissection of the lymph nodes in 20.

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61. Noble, T. P.: Carcinoma of the Penis in Siam, Brit. J. Urol. **5**:242 (Sept.) 1933.

When complete amputation was done the inguinal nodes were removed two weeks later. In cases of partial amputation these glands were removed at the time of operation. On histologic examination few of the nodes revealed metastasis, although most of them were enlarged. There was no operative mortality. The end-results are not given.

EPIDIDYMIS, SEMINAL VESICLE AND TESTIS

Cyst of Epididymis.—Patch [62] reported a case in which there was an intravaginal pedunculated cyst of the epididymis with torsion of the pedicle. The symptoms resembled those of torsion of the spermatic cord. At operation, in addition to a large hydrocele there was found within the vaginal sac a gangrenous cyst with a twisted pedicle which was attached to the head of the epididymis. There was a normal sessile hydatid of Morgagni. There were also incomplete descent of the testis and an inguinal hernia.

Patch considered the possible origin of this cyst. The vestigial structures associated with the testis and epididymis are: (1) the appendix testis, or sessile hydatid of Morgagni, a remnant of the müllerian duct attached to the upper pole of the testis or situated in the groove between the testis and the epididymis; (2) the appendix epididymidis, the stalked hydatid from the wolffian body attached to the globus minor; (3) the paradidymis, or organ of Giraldès, a collection of small tubules found above the head of the epididymis and in the lower end of the spermatic cord in front of the vessels; (4) the vasa aberrantia, or ductuli aberrantes, coiled canals with blind ends in the epididymis.

Torsion of the pedicle of any of these structures, especially of the sessile hydatid, may occur. Dix reported 46 cases in which there were symptoms resembling those of torsion of the spermatic cord, although of less severity. The condition usually occurs among patients between the ages of 11 and 14 years and probably is the syndrome often diagnosed as "idiopathic epididymo-orchitis" in children.

Spermatoceles are cysts in communication with the seminiferous system; they may be intravaginal or extravaginal, the latter type being more common.

The cyst under consideration evidently did not arise from either of the hydatids, from the paradidymis or from the superior vas aberrans. It was not openly connected with the seminiferous system, as it did not contain spermatozoa. It may have arisen from the inferior vas aberrans.

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62. Patch, F. S.: Pedunculated Cysts Within the Tunica Vaginalis, with Report of a Case Showing Torsion of the Pedicle, Brit. J. Urol. **5**:122 (June) 1933.

Vasitis.—Wolbarst [63] stated that the evidence that he presented shows that the vas deferens has a definite clinical identity. It may escape infection when infection is present at either end or surrounding it. It may be infected when there is no apparent infection at either end or surrounding it. Moreover, it may be a nidus for pyogenic organisms the presence of which in the vas deferens has not been reported previously. The author stated that influenza and other systemic infections may possibly be a frequent, unrecognized factor in the production of a focal infection in the vas deferens, with resulting stenosis and sterility.

URINARY ANTISEPTICS

Mitchell and Scott [64] studied the effect of urinary acidifiers and antiseptics on 75 patients who had urinary infections; surgical treatment was not indicated, nor had it been given to correct any factor accessory to the infection. The problem of acidification of the urine is important from the standpoint of its effect on infection and in conjunction with the use of methenamine. The criterion of cure was sterile urine on repeated culture. The specimens were obtained under sterile precautions and before breakfast in order to avoid the conflicting effect of a diurnal rise in hydrogen ion concentration. The patients in the first series were observed for four or five days without treatment in order to note the reaction of the urine and the bacterial counts. Various acidifiers were then given to change the p_H toward the acid side. Acid sodium phosphate was given in 20 grain (1.28 Gm.) doses four times a day. In only 1 case was there a downward trend of the p_H, and in none was the bacterial count improved. Acid ammonium phosphate, ammonium benzoate and ammonium chloride given in 20 grain doses four times a day were effective acidifiers, the shift to the acid side reaching a value as low as p_H 4.8 in some cases. To increase the acidity below this point, adventitious acids (ketonic) must make their appearance in the urine. In no case did the change in p_H modify the bacterial count.

Methenamine was then used in 10 grain (0.65 Gm.) doses four times a day in combination with ammonium chloride. In 19 of 50 cases of acute or chronic pyelocystitis cure was complete; that is, cultures were repeatedly negative. A large number of patients were practically cured but refused to cooperate further to complete the cure as it has been defined. Several considered as uncured were improved, as counts well in the millions were reduced to from 4 to 100 organisms per cubic centimeter. Even though the symptoms disappeared, the patients who dis-

63. Wolbarst, A. L.: The Vas Deferens, a Generally Unrecognized Clinical Entity in Urogenital Disease, J. Urol. **29**:405 (April) 1933.

64. Mitchell, D. R., and Scott, J. M.: Studies of Urinary Acidifiers and Antiseptics in Relation to Pyelitis and Cystitis, Brit. J. Urol. **5**:225 (Sept.) 1933.

continued treatment or of whom the authors lost trace were not included among those showing favorable results no matter how sure the progress to a complete cure.

Hexylresorcinol, methenamine and pyridium gave no evidence of having any value as urinary antiseptics.

In studying the failures, the following possibilities were considered: (1) that formaldehyde was not liberated rapidly enough to appear in any quantity at the level of the kidney; (2) that individual strains of organisms were resistant to formaldehyde; (3) that formaldehyde was absorbed by proteins in the urine, and (4) that there was persistence of a focus of infection (colonic absorption). Analysis for formaldehyde of specimens obtained by ureteral catheterization revealed only a slightly reduced amount as compared to that present in vesical specimens obtained simultaneously. This, together with the clinical cures in cases of pyelitis, suggests that methenamine is effective at the level of the kidney.

A definite resistance to formaldehyde was shown to be characteristic of certain strains of organisms, which accounted for the failure in some cases.

Colonic absorption seems to have a place in the etiology and treatment of persisting infections in the urinary tract. In these cases high colonic irrigations, with the administration of Bacillus acidophilus milk by mouth and of urinary antiseptics, were effective.

INFECTION OF URINARY TRACT

Winsbury-White [65] discussed the relation of infections of the genital tract to those of the urinary tract, not only in the lower part of the tract, where the relationship is obvious, but also in the upper part of the tract. In pyelonephritis and in other types of renal infection the possibility that infection of the genital tract is the source must be kept in mind.

Winsbury-White investigated the path by which genital and pelvic infections spread to the urinary tract. India ink, living bacilli of tuberculosis and dead bacilli of tuberculosis were injected hypodermically into the cervix in some cases and into the tissues of the urethra in others. Rabbits, rats and guinea-pigs were used; they were killed from one hour to three weeks after injection. Serial sections were made through the pelvic organs and the soft parts of the posterior pelvic and abdominal walls up to the hilus of the kidney.

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65. Winsbury-White, H. P.: The Spread of Infection from the Uterine Cervix to the Urinary Tract and the Ascent of Infection from the Lower Urinary Tract to the Kidneys, Brit. J. Urol. **5**:249 (Sept.) 1933.

In female animals extensions of infections as a result of injections into the cervix were found in the vesicovaginal septum, in the vesical wall and under the trigon. Extension upward took place through the lymph nodes of the broad ligaments and the posterior wall of the pelvis into the lymphatic structures which lie in such profusion at the level of the hilus of the kidneys, into the fatty areolar tissue in the hilus of the kidney and into the cortex itself. The leukocytic concentration of pigment in the cortex was outside the veins but in the perivascular lymphatic structures.

Injection into the urethral tissues produced the same results. These findings were in contrast to the picture when the infection was descending, with involvement of the glomeruli and capillaries.

Winsbury-White expressed the belief that the great majority of renal infections are ascending, extending from the genitals, the urethra or the vesical trigon along the pathways described, namely, the periurethral areolar tissue and lymphatic structures and the lymphatic structures in the posterior abdominal wall which empty into the lymphatic structures at the hilus of the kidney. He was convinced of this not only because of his injection experiments but because of his clinical experience. The cortex is involved through the lymphatic structures without primary involvement of the renal pelvis.

LESIONS OF GENITO-URINARY TRACT

Counseller [66] reported that in 1932 in the Mayo Clinic 1,186 operations were performed on 972 patients for lesions of the genito-urinary tract. These operations totaled 1,459 surgical procedures. There were 14 deaths—a mortality rate of 1.5 per cent. There were 228 operations on the kidney, 125 on the ureter, 172 on the bladder, 407 on the prostate gland, including transurethral resection, and 527 on the external genitalia. Of the 172 operations on the bladder, 33 were transvesical resections for carcinoma. The various surgical procedures consisted of cystostomy alone, segmental resection and excision, electrocoagulation, insertion of radium and a combination of these, including the use of the cautery. Two of these patients died.

Counseller recently reviewed the results of treatment at the clinic of 600 malignant tumors of the bladder. He found that 165 patients had lived from five to twenty years following various surgical procedures. In previous years electrocoagulation was generally confined to the treatment of infiltrating, highly malignant tumors usually situated at the base of the bladder and considered nonresectable. Seventeen of the 165 patients were treated by this method, and 15 (88 per cent)

66. Counseller, V. S.: Report of Urologic Surgery for 1932, Proc. Staff Meet., Mayo Clin. **8**:207 (April 5) 1933.

were alive and free from vesical symptoms at the time of the report. If these tumors are considered inoperable, the results indicate that the patients who lived less than five years and who were treated by electrocoagulation lived longer and in greater comfort than if such treatment had not been given. Electrocoagulation should, therefore, be considered in the treatment not only of very malignant inoperable lesions, but of those more favorably situated and less malignant. Furthermore, it may be made more effective by combining it with other procedures, such as partial excision of the growth or the insertion of radium. The latter method was used in approximately 50 per cent of the cases in the last year.

Counseller stated that 195 surgical procedures were performed on the kidney. These consisted of pelviolithotomy, nephrolithotomy, nephrostomy, nephrectomy, decapsulation, nephropexy and division and ligation of anomalous renal vessels for hydronephrosis. Four patients died —a mortality rate of 2.7 per cent.

Nephrostomy is being used with increasing frequency as a conservative procedure for temporary drainage of the kidney in cases of multiple renal calculi associated with infection and hydronephrosis. Its temporary use combined with plastic operations on the renal pelvis in cases of hydronephrosis is also advantageous. It has distinct advantages over pelviostomy: The tube can be changed easily, drainage ceases almost immediately following its removal and there is no distortion of the renal pelvis. Nephrostomy was performed in 26 cases as a procedure secondary to pelviolithotomy or nephrolithotomy for multiple renal stones, infection and hydronephrosis and in 2 cases of pyonephrosis in which sufficient renal parenchyma remained to justify a conservative type of operation. Temporary nephrostomy was carried out in a case of pyelonephritis. Nephropexy was performed in 9 cases as an aid to adequate drainage of the renal pelvis. Its use is distinctly indicated following division and ligation of anomalous renal vessels. It was performed in 3 such cases in this series with excellent results. There were no deaths.

Counseller stated that nephrectomy was performed in 95 cases: in 33 cases of unilateral renal tuberculosis; in 24 cases of nephrolithiasis in which the kidney was too severely injured to justify any conservative procedure; in 18 cases of extensive hydronephrosis in which the renal parenchyma was practically destroyed incident to anomalous renal vessels, and in 20 cases of malignant disease of the kidney. There were no deaths in this series.

In reporting the postoperative complications, Counseller stated that of the total group of 972 patients, 69 (7 per cent) had complications but only 1.7 per cent of these died. In 3 patients in whom complications developed, major surgical conditions other than urologic ones were present; these patients were excluded in the calculation of the mortality.

since the urologic procedures were minor and secondary. The total mortality rate, based on the number of patients and not on the number of surgical procedures, was 1.5 per cent.

MacKenzie and Seng [67] made a study of the cause of death in diseases of the genito-urinary tract; their investigation included all the deaths that occurred in the Department of Urology, Royal Victoria Hospital, over a period of fifteen years (265 in more than 11,000 cases). This gives a mortality rate of 2.39 per cent. For the same period, 5,064 major operations were performed, with 187 operative deaths; the operative mortality rate was 3.69 per cent.

The authors concluded that change in the genito-urinary tract of sufficient gravity to be the chief cause of death occurred in less than a third of the cases in the series, that cardiovascular and respiratory changes together were responsible for more than a third of the deaths and that all cardiovascular lesions, perhaps even arteriosclerosis at times, were grave conditions in the presence of serious disease of the genito-urinary tract. They expressed the belief that infection, whatever its source, within the genito-urinary tract or outside it, is a complication of the most serious consequence. The influence of infection, even if mild, on the cardiovascular and respiratory systems in the presence of disease of the genito-urinary tract is so grave as to constitute the "balance of power" between life and death. Almost two thirds of the deaths occurred in surgical conditions of the kidney and prostate gland; prostatism was the single disease entity revealing the greatest number of deaths, though it gave a comparatively low mortality rate.

The authors further concluded that new growths of the urinary bladder cause more than half of the deaths from neoplasms of the genito-urinary organs. The emergency surgical conditions of acute periurethral phlegmon with urethral stricture (extravasation) and rupture of the urethra call for the simplest and the most conservative surgical procedures at first, in order to reduce the high mortality rate.

White [68] stated that in this industrial age and with the vast increase in injuries caused by automobiles, trauma to the bladder and urethra, varying from slight abrasions of the mucosa to complete rupture and destruction of the lower part of the urinary tract, is being observed much more often than formerly. He stated that in general rupture of the urinary bladder is rare. It may be spontaneous, resulting from internal tension or forced injection of fluid or from intense muscular efforts in the presence of obstruction, inflammation or atony. It may

67. MacKenzie, D. W., and Seng, M. I.: Study of Cause of Death in Genito-Urinary Disease, J. Urol. **29**:321 (March) 1933.

68. White, E. W.: A Study of Certain Urological Complications Associated with Fractured Pelvis, J. Urol. **29**:295 (March) 1933.

be pathologic, caused by the invasion of tumors or by inflammatory processes spreading from organs in the vicinity. According to the recent literature, rupture of the bladder is becoming more common. It is often found in cases of trauma in which the pelvis is fractured. As far back as 1878, Bartels found 65 ruptured bladders in 169 cases of fracture of the pelvis. More recently, Campbell studied 166 cases of fracture of the pelvis at the Bellevue Hospital, New York. In 25 of these (15 per cent) the urethra was also ruptured, and in a number of others there was urinary distress. Campbell reported 55 cases of rupture of the bladder in 20 of which there was a concomitant fracture of the pelvis. In a study of 383 deaths resulting from automobile accidents alone, Bacon and LeCount found 42 cases of fracture of the pelvis, but in only 3 of these was there rupture of the bladder. They estimated that in 0.7 per cent of cases of automobile accidents the bladder is ruptured.

White stated that because of internal hydrostatic pressure rupture of the bladder can in most cases occur only when the bladder contains fluid. The distended bladder has a tendency to lean forward and upward; hence the inferior aspect is elevated and lifted toward the anterior abdominal wall. The base and the lateral and anterior walls are securely protected by the pelvis regardless of the vesical content. Violent force directed to the lower part of the abdomen if the bladder is distended invariably produces intraperitoneal rupture. As the upper portion of the inferior aspect of the bladder is the most movable and at the greatest distance from the point of impact, it is usually the site of rupture. Intraperitoneal ruptures are generally of the bursting type. Extraperitoneal rupture, owing to violent force directed toward the pelvis, takes place into the prevesical space; the surrounding tissues are promptly invaded by extravasated urine and blood, and certain definite objective symptoms are promptly noted.

White stated that the principal symptoms of rupture of the bladder are pain and tenderness over the pubes, vesical tenesmus, distention of the lower part of the abdomen, bloody urine and stoppage of urination; shock and vomiting may or may not be present. If the rupture is intraperitoneal, the pain soon becomes characteristic of intraperitoneal pain, and the usual signs of peritonitis are seen; if the rupture is extraperitoneal, the pain is localized in the lower part of the abdomen, radiating to the perineum and to the legs.

Since the advent of intravenous injections of iopax or neoiopax, the rule has been established that in all cases of suspected injury to the urinary tract intravenous pyelo-ureterograms are made at the earliest possible moment. Injuries to the kidney and ureters are clearly demonstrated if present. The complications likely to arise, whether rupture

of the bladder is extraperitoneal or intraperitoneal, are such that expectant treatment is only rarely justified, perhaps only in incomplete ruptures without evidence of urinary extravasation. In intraperitoneal ruptures, peritonitis and intoxication may be expected in at least half the cases. In extraperitoneal ruptures, extravasation of urine upward may be expected, as the triangular ligament prevents spreading into the perineum. Cellulitis and necrosis usually follow. When a rupture, whether intraperitoneal or extraperitoneal, is diagnosed, immediate operative intervention should be the rule, the first objective being to sidetrack the urine. Suprapubic cystotomy best fulfils all the needs, as it provides adequate drainage and puts the bladder at rest.

White stated that the urethra, like the bladder, may be ruptured by internal pressure, but that rupture is more usually caused by trauma due to blows on the perineum, to crushing of the urethra against the lower surface of the pubic arch or to laceration by spicules of bone from a fractured pelvis. Often, especially in industrial accidents, the rupture of the urethra is caused by what is known as a "straddle fall" on the perineum. The tear in the urethra may be longitudinal or transverse, complete or incomplete, extrapelvic or intrapelvic. In cases of very severe injury, the membranous urethra may be completely torn away from the bladder.

The usual symptoms of a ruptured bulbus urethrae are localized pain, urethral hemorrhage, perineal hematoma and retention of urine. The bleeding is from the meatus, independent of voiding, but when injury is proximal to the external sphincter the blood may remain in the posterior part of the urethra and find its way into the bladder. In intrapelvic rupture there is no perineal tumefaction, but marked ecchymosis usually develops after a time.

White further stated that the diagnosis of rupture of the urethra in the absence of rupture of the bladder presents practically no difficulties. Prompt surgical attack is the treatment of choice instead of costly delay and attempts at instrumentation. He stated the belief that preliminary cystotomy in a case of extensive laceration of the urethra is to be commended; the principle is basically sound.

White stated that until the bladder is opened it is often not possible to distinguish between an extraperitoneal tear of the bladder and an intrapelvic rupture of the urethra. The general guiding rule in diagnosis is that if the bladder is even moderately distended the rupture must be situated below the vesical sphincter. The prognosis of the operative treatment of rupture of the urethra is excellent as regards life but not favorable as regards function. Young reported in detail 9 cases of rupture of the urethra associated with fracture of the pelvis. In these cases the importance of operation was noted, including accurate

repair of the urethra to avoid subsequent complications or death. With early operation, excellent results and absence of complications may be expected in the majority of cases. The postoperative treatment in all cases is important; regular and systematic dilations of the urethra are advised for an extended time, in order to assure good functional results in the future.

Early diagnosis and prompt and intelligent surgical intervention have been of inestimable value in the restoration of life and function in cases of injuries to the pelvis and urethra. Formerly, delay and neglect resulted in irreparable gross advanced pathologic changes, extreme destruction of tissue, osteomyelitis, pelvic cellulitis and gangrene, thrombophlebitis causing septicemia and multiple abscesses.